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FACILE SYNTHESIS OF (3aS)-1,3a-DIMETHYL-2,3,3a,5,6,7-HEXAHYDROINDEN-4(5H)-ONE, AN INTERMEDIATE FOR STEROID SYNTHESIS[1]

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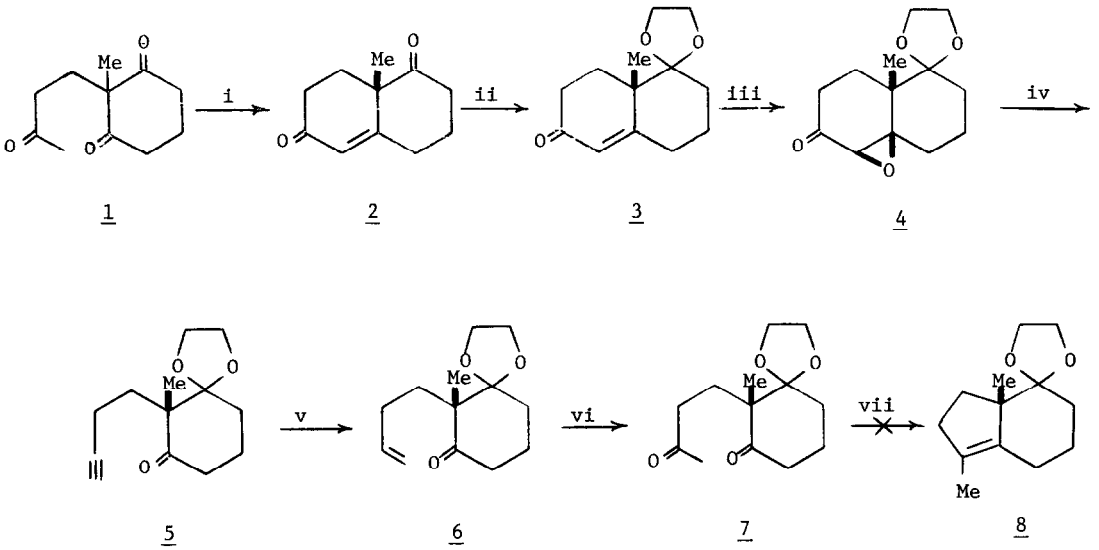
Abstract: The optically active Wieland-Miescher ketone 2 has been converted in six steps to the enone 9, a potentially useful synthon for optically active steroid and terpene synthesis.

Studies on new approaches to the total synthesis of steroids continue unabated. Recently several new routes to racemic[4] and optically active[5] steroids have been described. We wish to report here a facile synthesis of an optically active hydrindenone in good yield which should be quite useful as an AB-ring synthon for steroid synthesis.

Of the several possible optically active AB-ring synthons for steroid synthesis and, in particular, corticosteroid synthesis, it was decided to use a dimethyl-substituted hydrindenone such as 9. It was reasoned that after the attachment of the C and D rings, the simple process[6] of ozonolysis followed by base treatment would produce the desired enone functionality in ring A. For these reasons, compound 9 (and its ketal 8) was our immediate target.

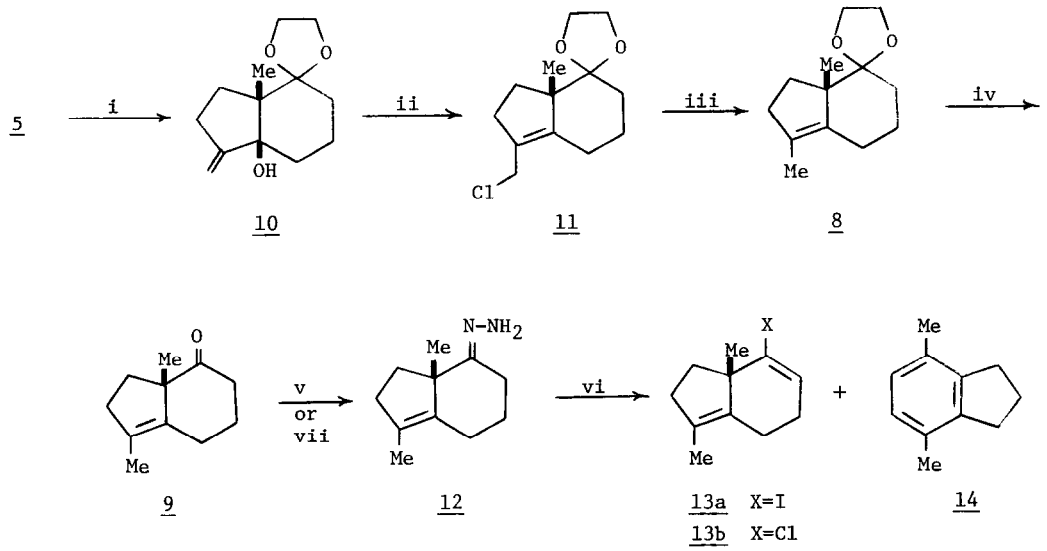
Soon after the report of Hajos and Parrish on the use of S-proline for asymmetric induction in the cycloaldolization of 2-(3-ketobutyl)-2-methylcyclopentane-1,3-dione,[7] Furst and coworkers[8] applied the method to the synthesis of the octalin dione 2 (Scheme 1). Cyclization of the readily available trione 1 with S-proline produced the optically active enedione 2 in 72% yield with reasonably good enantiomeric excess (71% ee). Optically pure 2 could be obtained from this enriched material by careful recrystallization.[8] Selective ketalization of 2 to give 3 is known.[9] We originally considered the diketone ketal 7 as an immediate precursor to 8. Thus before reclosure, the A ring must be cleaved; for this process, an Eschenmoser-Tanabe fragmentation[10] seemed the best possible procedure. Epoxidation of 3 with basic hydrogen peroxide gave the ketoepoxide 4 in 70% yield [mp 143-5°C, $[\alpha]_D^{25}$ = +124°($CHCl_3$), correct analysis].[11] A cooled solution of 4 (CH_2Cl_2/AcOH) was treated with tosyl hydrazide in the presence of solid sodium carbonate[12] to furnish the keto acetylene 5 [mp 56.5-59.5°C, $[\alpha]_D^{25}$ = -62.7° ($CHCl_3$), correct analysis] in 78% yield. Selective hydrogenation of the acetylene was carried out over Lindlar catalyst to produce in 90% yield the terminal olefin 6 [mp 32-4°C, $[\alpha]_D^{25}$ = -77.5° ($CHCl_3$), correct analysis] which was oxidized under the conditions of Tsuji[13] for the Wacker oxidation to give the methyl ketone 7 [colorless oil, $[\alpha]_D^{25}$ = -46.7°($CHCl_3$)]. However attempted intramolecular coupling of the diketone ketal 7 using McMurry's conditions[14] ($TiCl_3$, Zn-Cu couple, DME, reflux, 24h) was unsuccessful due to the instability of the ethylene ketal under these conditions.[14] Therefore this route to 8 was abandoned.



Scheme 1. i) S-proline DMSO, 25°C, 24h, 72%, 71%, ee; ii) ethylene glycol, pTsOH, Δ; 80%; iii) H_2O_2, NaOH, 68%; iv) pTsNHNH$_2$, AcOH, CH_2Cl_2, K_2CO_3 (solid); 78%; v) H_2, Lindlar, 90%; vi) $PdCl_2$, CuCl, O_2, 81%; vii) $TiCl_3$, Zn-Cu couple, DME, reflux, 24h.

An alternative route to the hydrindenes 8 and 9 was devised using the reductive cyclization of δ,ε-acetylenic ketones developed by Stork[15] for the construction of the desired 5,6-fused skeleton (Scheme 2). Treatment of the acetylenic ketone 5 with sodium in liquid ammonia in the presence of excess ammonium sulfate as a proton source produced the allylic alcohol as a single stereoisomer which is assigned the cis stereochemistry 10 [oil, $[\alpha]_D^{25} = -20.0°(CHCl_3)$]. A rapid allylic rearrangement of 10 was effected upon chlorination with thionyl chloride in pyridine to give the primary allylic chloride 11 [oil, $[\alpha]_D^{25} = +46.1°(CHCl_3)$] which was reduced directly with lithium aluminum hydride in refluxing ether to afford the desired ketal 8, [oil, $[\alpha]_D^{25} = +13.7°$ ($CHCl_3$), HRMS] in 42% overall yield from 5. Hydrolysis of the ketal (1N HCl/acetone) gave the desired optically active AB-ring synthon 9 [colorless liquid, $[\alpha]_D^{25} = +35.1°(CHCl_3)$, HRMS] in 88% yield thus ending a short and efficient synthesis (6 steps from 3, 20% overall yield).

For use in our anionic oxy-Cope rearrangement approach to steroid synthesis,[16] we required a vinylic nucleophile derived from the ketone 9. Several methods exist for the conversion of ketones to vinyl halides[17] or to the vinyl anion directly.[18] As an initial method, we examined the conversion of 9 into the vinyl halides 13ab. Treatment of the hydrazone 12 (prepared from the ketone 9 in 82% yield) with 2 equivalents of iodine in the presence of excess triethylamine[17a] (followed by treatment with potassium t-butoxide) produced a mixture of the desired vinyl iodide 13a and the interesting rearrangement product, 4,7-dimethylindane 14.[19] This rearrangement also



Scheme 2. i) Na, NH_3, $(NH_4)_2SO_4$, 90% crude; ii) $SOCl_2$, pyr, 82% crude; iii) $LiAlH_4$, Et_2O, reflux, 6h, 42% overall from 5; iv) 1N HCl, H_2O, acetone, 88%; v) H_2NNH_2, EtOH, 82%; vi) 2eq I_2, xs Et_3N, Et_2O, 25°C, 6h, 7% 13a, 28% 14; vii) Ph_3P, CCl_4, heat, 10h, 42% 13b, 21% 14.

occurred under other conditions to generate vinyl halides[17c] (e.g., PPh_3, CCl_4, heat) giving the vinyl chloride 13b and 14 in somewhat different yields.[19] The use of these vinyl halides and related vinyl anions in steroid synthesis is under way and will be described in due course.[20]

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References and Notes

(1) Presented at the 14th Sheffield Stereochemistry Conference, Sheffield, England, December 1980, and at the 4th International Conference on Organic Synthesis, Tokyo, August 1982.

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(11) All new compounds exhibited 200 MHz ^{1}H NMR, ^{13}C NMR, IR and MS in complete agreement with their assigned structures. Moreover, crystalline materials exhibited correct elemental analyses while non-crystalline materials gave correct high resolution mass spectra (HRMS).

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