# SIMPLE REGIOSELECTIVE SYNTHESIS OF TRANS-7a-METHYLHYDRIND-4-EN-1-ONE,

## A KEY INTERMEDIATE FOR STEROID TOTAL SYNTHESIS[1]

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Abstract: Intramolecular Diels-Alder cycloaddition and hydrolysis of the ketals 11 and 12, derived from the trienone 6, afforded mainly the trans-hydrindenone 8a.

The last few years have witnessed a great upsurge in interest in the development of new methods for the total synthesis of steroids.[4] Most of the new routes have been designed to produce A-ring aromatic steroids such as estrone,[5] although a few have been aimed at the more medicinally interesting corticosteroid group, e.g., cortisone 1.[6] We report here a very simple method for the stereoselective preparation of the key trans C,D-ring intermediate 8a for the total synthesis of steroids.
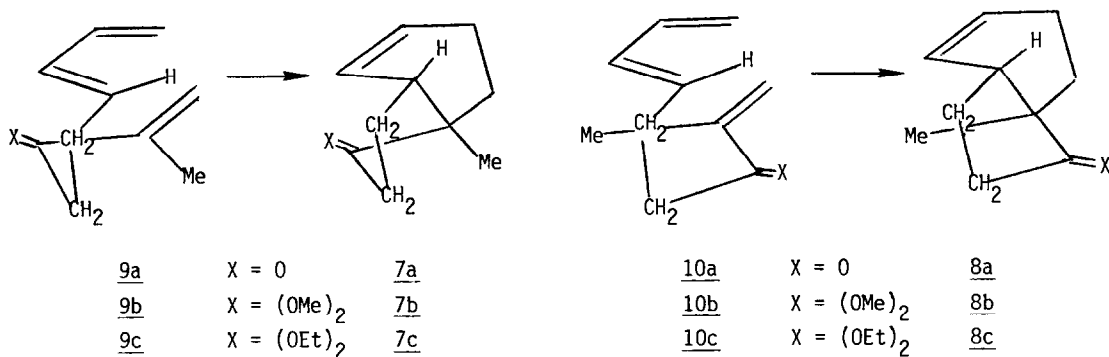
For some time, we have envisioned the approach shown retrosynthetically in Scheme I, namely the preparation of cortisone 1 by standard methods from the dione 2 which could itself be produced from a Diels-Alder reaction of the diene 3[7] with the hydrindenedione 4.[8] This key enedione might be prepared by any of several methods, one of the simplest and most intriguing being the intramolecular Diels-Alder addition of either of the two acyclic trienones, 5 or 6, followed by oxidation to the ketone. Thus, it was decided to investigate this expedient route, namely the cyclization of 6 and its derivatives.

Sutherland[9] reported several years ago that heating of 6 in benzene at 190°C for 13 hours afforded an 85% yield of a mixture of three products in a ratio of 30:4:3. The major product, isolated by preparative gas chromatography (GC), was shown to be the cis hydrindenone 7a, while the other two products were not identified. This result seemed somewhat peculiar in view of our recent work on related systems leading to the total synthesis of coronafacic acid,[10] in which significant amounts of the trans hydrindenone were also produced. Therefore, Sutherland's experiment was repeated under various sets of conditions with somewhat different results. Heating of a solution of 6 in benzene (190°C, 13h) or toluene (170°C, 24h) produced a 99% yield of a mixture of the two cyclized products, 7a and 8a. The ratio of the two products was calculated to be approximately 70:30 favoring the cis by careful integration of the two methyl peaks in the 200 MHz $^1$H NMR spectrum. In the cis compound 7a, the methyl appears as a singlet at 1.042δ[9] while in the trans isomer 8a, the methyl is a small doublet at 0.893δ (W-coupling of 0.7Hz to the proton at the ring juncture). To show that these structural assignments were indeed correct, pure samples of each adduct were isolated by preparative GC or, more easily, by HPLC (Waters 500) using EtOAc/hexane and hydrogenated to the known cis (methyl
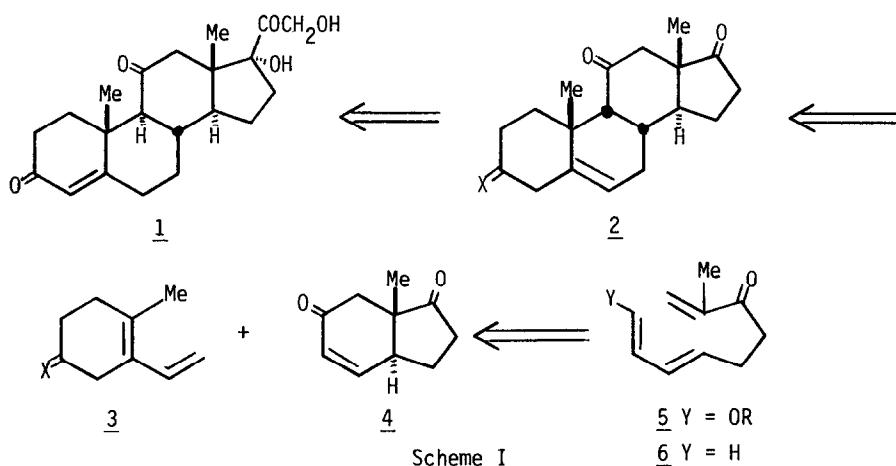
Scheme I

at 1.041δ) and <u>trans</u> (methyl at 0.873δ) hydrindanones[11] (yield of hydrogenation, 81%).

Examination of molecular models or three-dimensional drawings (Scheme II) helps one to understand why such high temperatures are required for this cyclization (negligible cyclization in toluene or chloroform solution at temperatures ranging from 25°C to 130°C, even in the presence of acids and/or metal ions) when compared to corresponding cycloadditions in the 1-octalone series (cyclization at 0°C or 25°C, in the presence of acids and/or metal ions).[12] In the <u>endo</u> transition state for cyclization <u>9a</u>, the carbonyl group does not overlap well with the olefin and thus this enone is not as good a dienophile as it would be in an intermolecular reaction. One would also surmise that this non-planarity of the enone system causes the favorable "secondary overlap" leading to the normal stability of the <u>endo</u> transition state to be weakened here. Since the enone is "non-conjugated" in the transition state for cyclization, the system resembles a simple triene and thus requires very high temperatures for cyclization. It is interesting to point out that the addition of one methylene unit to the chain allows the carbonyl to overlap effectively with the olefin in the transition state for cycloaddition so that the cycloaddition occurs at 0°C and gives complete <u>endo</u> stereospecificity in the 1-octalone formed.[12]



| <u>9a</u> | X = O | <u>7a</u> | | <u>10a</u> | X = O | <u>8a</u> |
| <u>9b</u> | X = (OMe)$_2$ | <u>7b</u> | | <u>10b</u> | X = (OMe)$_2$ | <u>8b</u> |
| <u>9c</u> | X = (OEt)$_2$ | <u>7c</u> | | <u>10c</u> | X = (OEt)$_2$ | <u>8c</u> |

Scheme II

Since the carbonyl apparently does not contribute much to lowering the activation energy of the cycloaddition, it was conjectured that its derivatives would cyclize at about the same temperature. More importantly, it was predicted that simple ketals might cause the cyclization to occur via the exo transition states. For example, the endo transition states 9b and 9c should now experience significant steric interference between one of the two alkoxy groups and the butadiene system. The corresponding exo transition states, 10b and 10c, might therefore be more stable with the methyl group in the endo position in place of the dialkoxymethylene group. The prediction proved to be true.

Ketalization of the trienone 6 with trimethyl orthoformate in methanol with acid catalysis gave the corresponding ketal 11 in good yield. Heating of 11 at 170°C in toluene for 24h produced a 98% yield of the adduct as a mixture of the ketal and enol ether. Direct hydrolysis of the crude reaction gave a mixture of 7a and 8a in which the trans isomer now predominated in a 28:72 ratio. Thus, the regioselectivity is reversed by simply making the carbonyl center more sterically demanding than the methyl group. The sequence was repeated with the diethyl ketal 12 in the hope that the
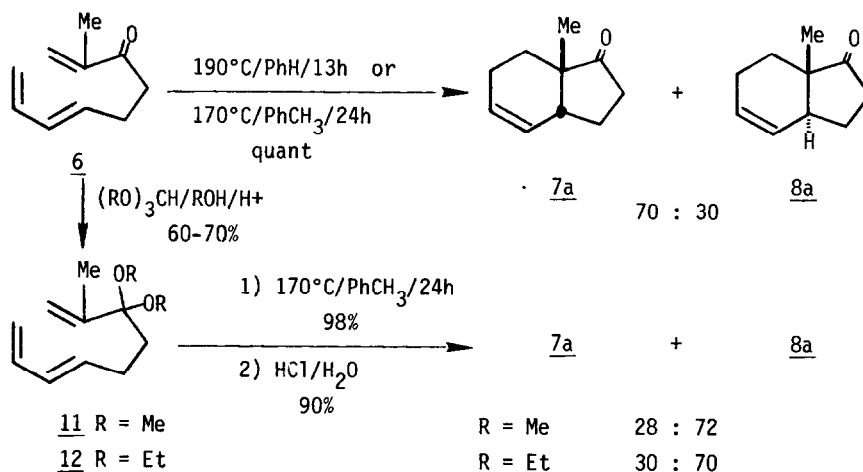


slightly additional steric bulk might cause additional stereoselectivity. However, cyclization of 12 followed by hydrolysis gave an essentially identical mixture of 7a and 8a in very high yield.[13]

Thus, by simple modification of the readily available trienone, one can stereoselectively prepare trans hydrindenones as potential CD-ring intermediates for steroid synthesis. We are currently attempting to increase the stereoselectivity of cycloadditions of this type by the cyclization of more sterically demanding ketone derivatives (aminals, thioketals, etc.) as well as using bulky optically active Lewis acid catalysts and various acetyl alkoxy derivatives closely related to the C-17 functionality in cortisone.[14]

## REFERENCES AND NOTES

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8. Addition of 3 and 4 should produce the stereochemistry (approach of diene from less hindered side and Alder's endo rule) and regiochemistry (Houk's molecular orbital coefficient analysis) shown in 2 as the major product.

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13. The tetramethylethylene ketal corresponding to 11 could be formed in modest yield from 11 and pinacol in benzene with acid catalysis. Its intramolecular cycloaddition required three days of heating at 170°C and produced after acidic hydrolysis, an approximately 1:3 mixture of 7a and 8a in 97% yield. It should be pointed out that Prof. Paul Helquist has observed similar stereoselectivity in the internal cyclization of another ketal of 6; see accompanying paper.

14. An additional proposal for increasing the stereoselectivity involves having a bulky substituent at the 7-position of the 1,6,8-trien-3-one, as in cyclizations leading to coronafacic acid.[10,15] For example, intramolecular cycloaddition of the compound corresponding to 11 in which the C7 and C8 hydrogens have been replaced by a tetramethylene unit (i.e., a 1,2-alkylidene methylene cyclohexane) would be expected to afford more of the trans isomer due to increased steric interaction between the ketal functionality and the methylene group attached to C7. This is being tested currently.

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