

STERESELECTIVITY IN INTRAMOLECULAR DIELS-ALDER REACTIONS;

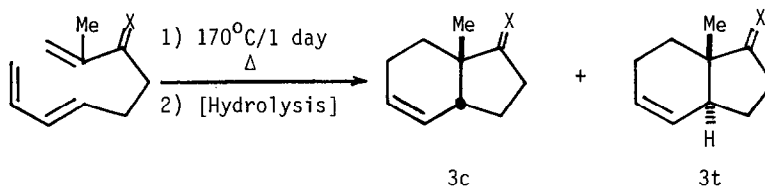
A SHORT TOTAL SYNTHESIS OF (+)-ESTRONE¹

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Summary: A new synthesis of estrone via an internal Diels-Alder reaction is reported.

Recently major advances have been made in controlling ring-juncture stereochemistry in intramolecular Diels-Alder reactions of 1,3,8-nonatriene and 1,3,9-decatriene derivatives. Especially noteworthy have been the contributions of Roush,^{4a} Boeckman,^{4b} Taber,^{4c} Nicolaou,^{4d} Parker,^{4e} Wilson,^{4f} White,^{4g} Fuchs,^{4h} Ley,⁴ⁱ and others. Last year we reported^{5a} that the 3:1 cis-stereoselectivity observed in the thermally-promoted cyclization of E-8-methyl-1,3,8-nonatriene-7-one 1 could be changed to 3:1 trans-stereoselectivity by cyclization of the dimethyl ketal of 1, 2, leading to the trans-indenone 3t (X=O) in 70% isolated yield. We now report an increase in the trans-stereoselectivity of the reaction due to an alkyl substituent at C3 of nonatrienes such as 1 and the application of this approach to a short total synthesis of (+)-estrone.



<u>1</u> X = O	95%	3 : 1
<u>2</u> X = (OMe) ₂	98%	1 : 3
<u>4</u> X = S(CH ₂) ₃ S	96%	47 : 53

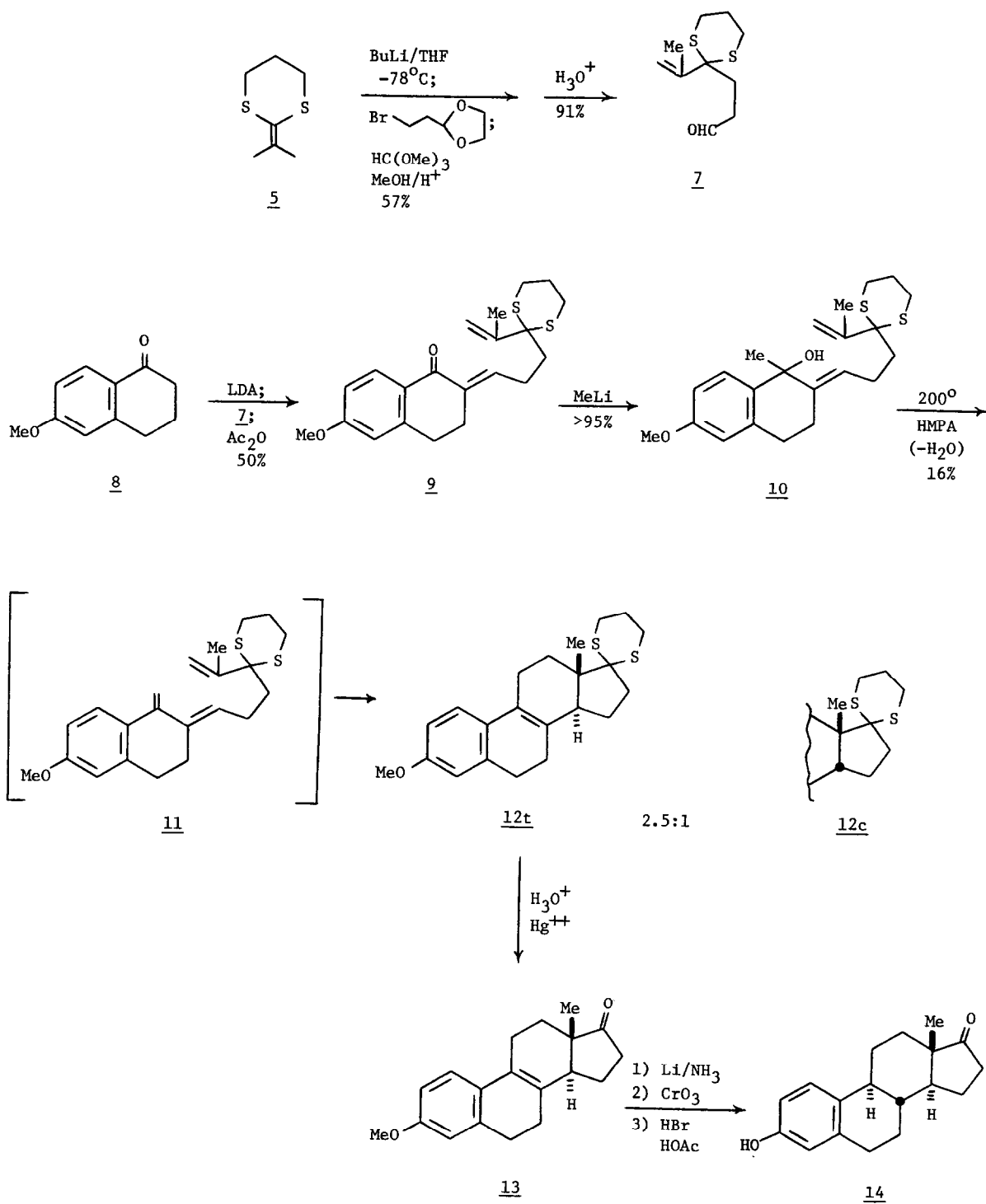
The dithiane 4 was prepared to test the effect of thioketals on the cis/trans-selectivity of the cycloaddition. Heating 4 at 170°C for 24 hr gave a 96% yield of a 47:53 mixture of the thioketals of 3c and 3t. Thus the dithiane group exerts a trans-directing influence vs. the ketone but not nearly as strong as that of the ketals. As we argued in our earlier paper,^{5a} a substituent at C3 of 1 should increase the steric interactions between the ketal or thioketal substituent in the transition state leading to the cis ring juncture but not in that leading to the trans, and thus improve the trans-selectivity.

As a test of this hypothesis, we proposed the cycloaddition of a 1,3,8-nonatriene with substituents at both C2 and C3, namely the triene 11, the product of which 12t would be easily

converted into (+)-estrone **14** (Scheme I). The ketene bithioacetal **5** (easily prepared from acetone and dithiane⁶) was deprotonated and alkylated with the bromoacetal **6** (prepared from treatment of acrolein with HBr in ethylene glycol⁷) to give only the product of α -alkylation. Transketalization followed by acidic hydrolysis produced the aldehyde **7** in 52% overall yield.⁸ Formation of the anion of commercially available 6-methoxy-1-tetralone **8** followed by addition of **7** and then acetic anhydride produced only the E-enone **9** in 48% yield with 44% of the starting material recovered. The olefination of **9** to give **11** proved extremely difficult. The normally successful methods--Wittig reaction, Tebbe reagent, silyl-Wittig reaction--all failed for various reasons. For example, trimethylsilylmethyl lithium reacted facily with E-2-butylidene-1-tetralone to give the trimethylsilylmethyl alcohol which lost the elements of trimethylsilanol on flash chromatography to give the diene analogous to **11** in very high yield. Evidently the 6-methoxy group decreases the ketone reactivity sufficiently to render it inert to reaction with the trimethylsilylmethyl lithium.⁹ In order to test the general approach we resorted to a somewhat unsatisfactory alternative, namely thermal dehydration of the tertiary carbinol. Addition of methyl lithium to **9** proceeded in nearly quantitative yield to give **10** which was pyrolyzed in HMPA at 210°C for 5 hr to effect dehydration to **11**¹⁰ and subsequent cyclization to give a mixture of **12t:c**. Separation on silica gel afforded a 2.5:1 mixture of **12t:12c** in 16% overall yield from **9**. Comparison of this regioselectivity (**t:c** = 2.5:1) to that observed with the parent thioketal **4** described above (**t:c** = 1:1) implies that the introduction of a methylene group at C3 of the triene destabilizes the endo transition state (TS_N) relative to the exo transition state (TS_X) presumably due to a greater increase in the steric interaction in the former. That this interaction is still effective in improving the trans-stereoselectivity even at 200°C is noteworthy.



The synthesis of estrone **14** from **12t** was finished in short order. Mercuric ion-assisted hydrolysis of the thioketal produced in 53% yield the known enone **13**.¹¹ This compound has been converted to estrone by a three-step route, namely dissolving metal reduction, reoxidation at C17,



Scheme I

and methyl ether hydrolysis,¹² to give 14 in 50% overall yield. The brevity of this estrone synthesis makes up somewhat for its low overall yield. Attempts to better the olefination of the enone and to further improve the trans-stereoselectivity of the cycloaddition are underway.

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References and Notes

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- (3) Winstein Dissertation Fellow, 1982; Chevron Fellow, 1980-1981.
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- (6) P. F. Jones and M. F. Lappert, J. Chem. Soc. Chem. Commun., 526 (1972).
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- (8) This compound could also be prepared in only three operations in 49% overall yield by alkylating the anion of 5 with the dimethyl ketal followed by hydrolysis.
- (9) The use of trimethylsilylmethylsodium or -potassium did not improve this reaction. Many other alternatives, e.g., the anion of methylenetriphenylphosphorane, various combinations of dibromomethane, metals and Lewis acids, etc., were also tried unsuccessfully.
- (10) Several other methods for the dehydration of tertiary alcohols, e.g., heating on alumina, thionyl chloride or phosphorus oxychloride in pyridine, etc., also proved unsatisfactory.
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