

STERESELECTIVITY IN INTRAMOLECULAR DIELS-ALDER REACTIONS;

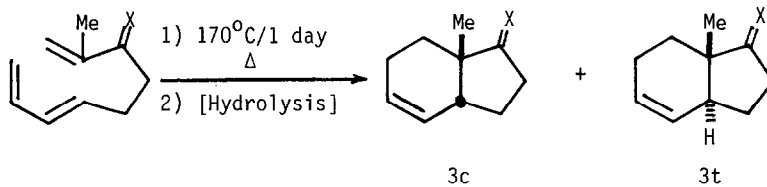
A SHORT TOTAL SYNTHESIS OF (+)-ESTRONE¹

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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.

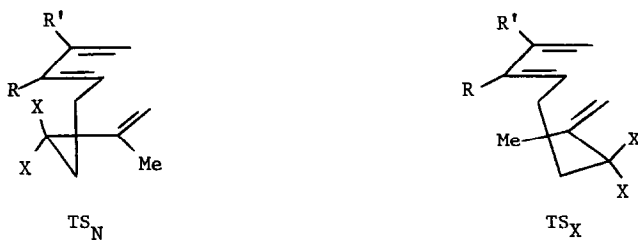


1 X = O	95%	3 : 1
2 X = (OMe) ₂	98%	1 : 3
4 X = S(CH ₂) ₃ S	96%	47 : 53

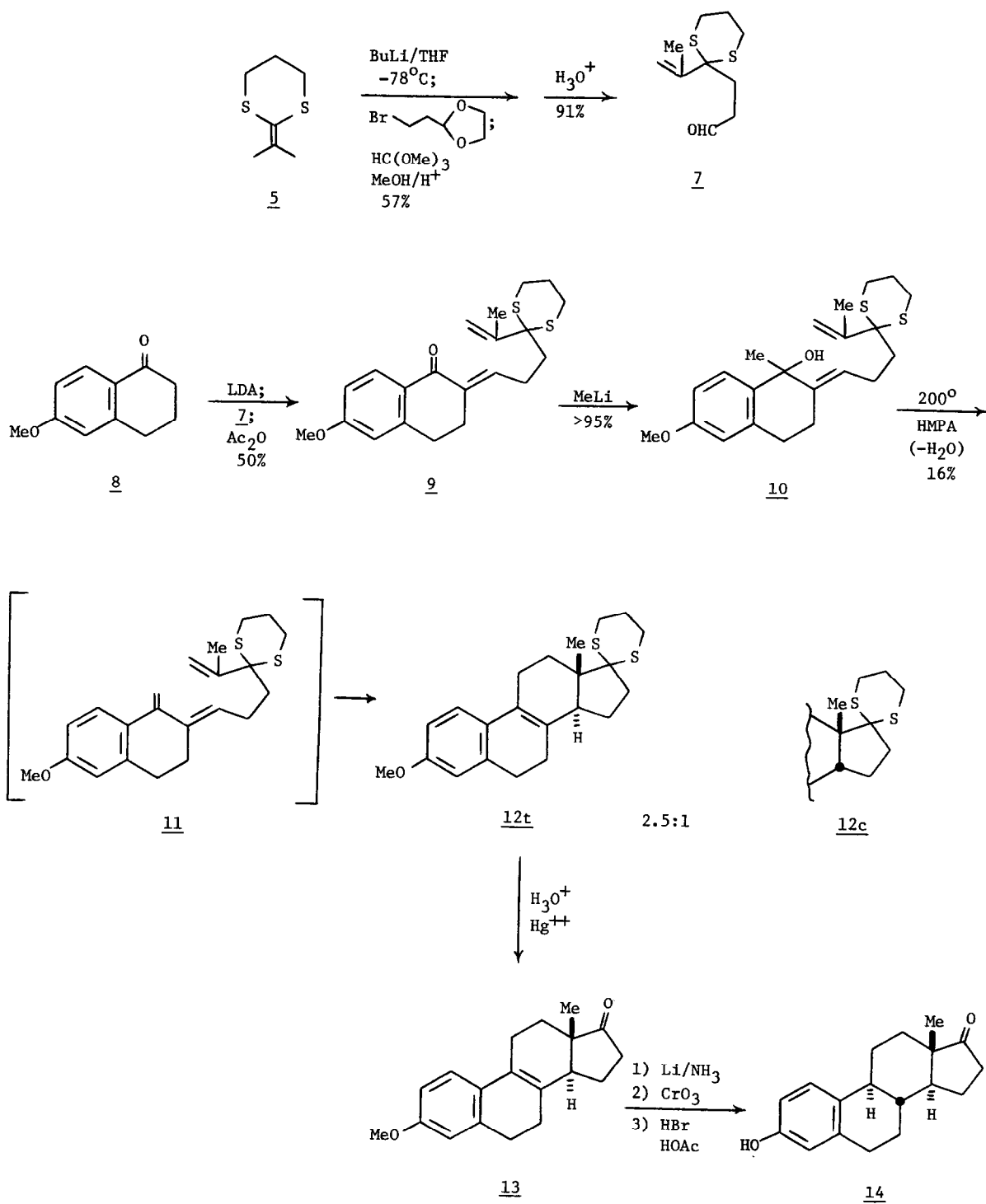
The dithiane **4** was prepared to test the effect of thioketals on the *cis/trans*-selectivity of the cycloaddition. Heating **4** at 170°C for 24 hr gave a 96% yield of a 47:53 mixture of the thioketals of **3c** and **3t**. Thus the dithiane group exerts a *trans*-directing influence vs. the ketone 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 facilely 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

- (1) Presented at the IUPAC 4th International Conference on Organic Synthesis, Tokyo, August 1982.
- (2) Camille and Henry Dreyfus Teacher-Scholar, 1978-83; A. P. Sloan Foundation Fellow, 1979-81.
- (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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