Tetrahedron Letters, Vol.31, No.28, pp 4027-4028, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

STEREOSELECTIVE CONSTRUCTION OF STEROIDAL TRANS-HYDRINDANES VIA INTRAMOLECULAR ESTER ENOLATE ALKYLATION[1,2]

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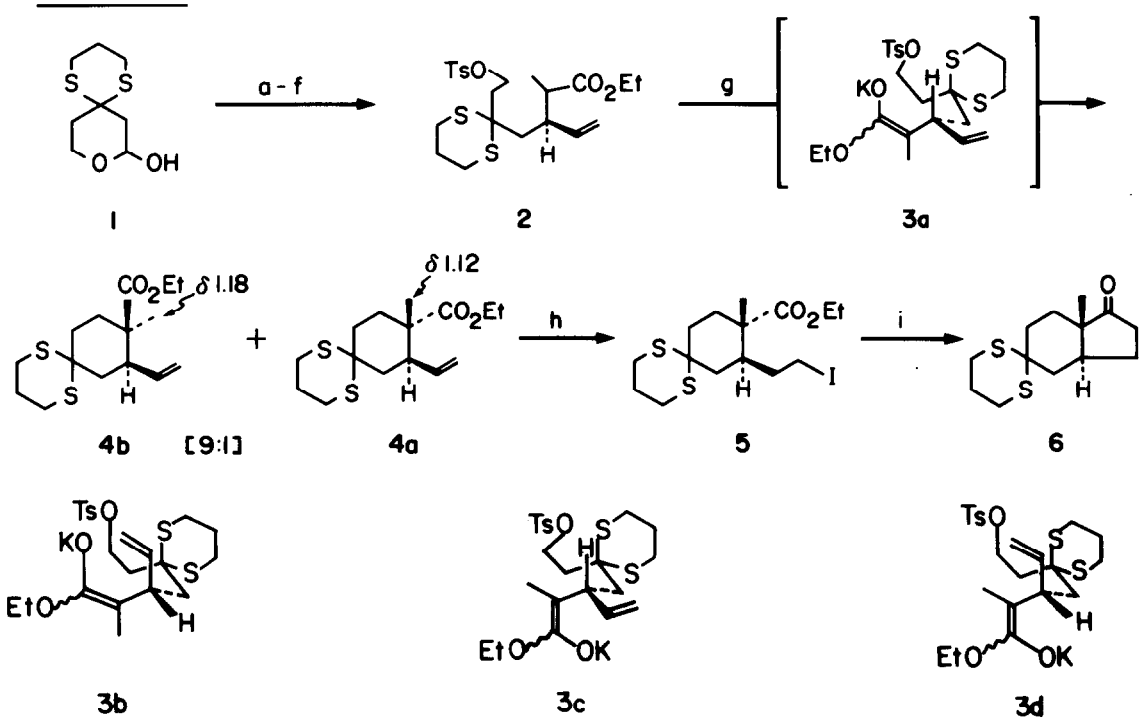
Summary: Steroidal trans-hydrindanone 6 was stereoselectively synthesized from lactol 1 in nine steps in 27% overall yield via intramolecular ester enolate alkylation methodology.

The trans-fused CD ring systems found in most steroids have served as attractive targets for organic chemists and have played a very important role in the development of new synthetic methodologies, notably exemplified by Stork's work in this area.[3] In this note we wish to describe our recent progress in the stereoselective construction of steroidal trans-hydrindanes based upon our intramolecular ester enolate alkylation strategy[4], as shown in SCHEME I.

SCHEME I



Reagents: a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, reflux, 6h (96%); b) TBDPS-Cl, imidazole, DMF, rt, 3h (100%); c) DIBAL, toluene, -70 °C, 1h (84%); d) $CH_3CH_2C(OEt)_3$, phenol, 160 °C, 6h, (89%); e) $(n\text{-}Bu)_4NF$, THF, rt, 3h (93%); f) TsCl, pyridine, $CHCl_3$, 0 °C, 1h (97%); g) KHMDS, THF, -78 to -20 °C, 4h (82%); h) DCB, THF, 0 °C to rt, 1h, then, ICl, NaOAc, MeOH, rt, 30 min (65%); i) t-BuLi(2 eq), ether, -100 to -50 °C, 1h (85%)

Key internal alkylation substrate 2 was prepared from known[4b] lactol 1 in a straightforward six-step Claisen-Wittig sequence in 65% overall yield. Cyclization of ester 2 with KHMDS in THF at -78 to -20 °C for 4 h furnished a 9 to 1 mixture of cis- and trans-dialkylcyclohexanecarboxylates 4a and 4b in 82% total yield, presumably via the more stable 'H-eclipsed' transition state geometry of the ester enolate as shown 3a rather than 'vinyl-eclipsed' or 'bisected' transition state geometries 3b-d .[5,6,7]

Major isomer 4a was converted into trans-hydrindane 6 in two steps; the vinyl group was hydroborated with dicyclohexylborane followed by treatment with iodine monochloride and sodium acetate[8] to afford the primary iodide 5 in 65% yield, which was subjected to metal-halogen exchange-initiated anionic cyclization[9] to give the desired trans-hydrindane 6 in 85% yield.[6,10]

In conclusion we have demonstrated the potential of our intramolecular ester enolate alkylation protocol by efficiently synthesizing steroidal trans-hydrindane 6 in a steroselective manner. Efforts are being made in our laboratories to refine our IEEA route to various steroidal trans-hydrindanes with particular emphasis on the improvement of stereoselectivity, which will be disclosed in due course.

ACKNOWLEDGEMENTS: We gratefully acknowledge the Korea Science and Engineering Foundation for a generous financial suppport. We are deeply indebted to Dr. M. Y. Kim (Dong-A Pharmaceutical Co.) for her assistance in obtaining high-field NMR spectra.

REFERENCES AND NOTES

1. Dedicated to Professor Won-keun Chung on the occaison of his 60th birthday.
2. This work was presented at the first U. S. A.-Korea Joint Seminar on New Methods in Organic Synthesis, 1988, Seoul, Korea
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5. The ratio of steroisomers of 4 was determined both by isolation by SGC and by capillary GC analysis (0.2 mm i.d. x 50 m long CBP-1 column, 250 °C).
6. Compound 4a : IR (neat) ν 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 1.12 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 13.78, 25.37, 25.47, 25.71, 31.30, 32.24, 37.42, 40.72, 45.54, 48.79, 59.76, 115.21, 137.88, 176.02. Compound 4b : IR (neat) ν 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 1.18 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 14.08, 25.52, 25.81, 25.89, 26.08, 33.11, 34.77, 40.23, 45.22, 46.70, 49.59, 59.86, 116.13, 139.00, 147.93. Compound 6 : IR (neat) ν 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.40, 23.40, 25.97, 26.04, 26.50, 28.04, 33.79, 35.56, 37.45, 40.10, 47.71, 50.12, 219.37; MS(CI-Me) m/z 257 (M+1)
7. For a similar explanation, see: K. Asao, H. Iio, and T. Tokoroyama, Tetrahedron Lett., 30, 6397 (1989) and references cited therein.
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9. T. van der Does, G. W. Klumpp, and M. Schakel, Tetrahedron Lett., 27, 519 (1986) and references cited therein.
10. Stereochemistry of 6 was confirmed by conversion into the corresponding diketone by treatment with excess MeI in aqueous acetonitrile. We thank Professor T. Takahashi (Tokyo Institute of Technology) for providing us with NMR spectra of the authentic diketone.

(Received in Japan 12 March 1990)