Tetrahedron Letters,Vol.25,No.12,pp 1231-1234,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

A VINYLSILANE ROUTE TO TRANS-7a-METHYLHYDRIND-4-EN-1,6-DIONE

Scott E. Denmark* and Juris P. Germanas

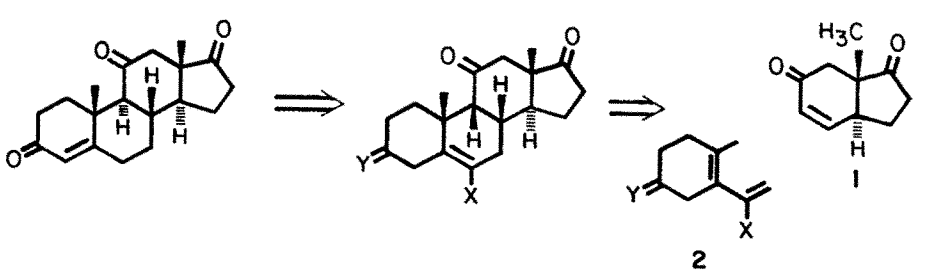
Roger Adams Laboratory, School of Chemical Sciences,
University of Illinois, Urbana, Illinois 61801

Summary: A stereoselective synthesis of the title compound is described. The overall yield is 34% starting with 2-methyl-2-cyclopentenone. The trans ring-fusion stereochemistry is established by a conjugate addition/trapping sequence.

Steroids with oxygen functionality in the 11-position (adrenocorticosteroids) are among the most important regulatory hormones controlling such functions as water and mineral balance, protein and carbohydrate metabolism and inflammation of tissues associated with injuries, allergic reactions and auto-immune processes.[1] Classic solutions to the problems presented by this class of steroids range from the landmark syntheses of aldosterone and cortisone[2] to the microbiological oxidation[3] of desoxy precursors. Recently there has been a resurgence of interest in the total synthesis of 11-oxosteroids. In particular, Stork has recently reported several new approaches to this system involving reductive alkylation of enediones[4a,b] or an intramolecular Diels-Alder reaction.[4c] The introduction of the 11-oxygen substitutent is intimately associated with the processes mentioned above. However, the success of those approaches also serves to illustrate the power of two new and highly selective methods for the preparation of suitably functionalized trans-hydrindanone precursors.[5]

A conceptually different approach to 11-oxosteroids which represents an A + CD → ABCD approach, shown in Scheme 1, has the advantage of incorporating the requisite 11-oxygenation in the trans-hydrindenone subunit where it may also serve an activating function for the critical

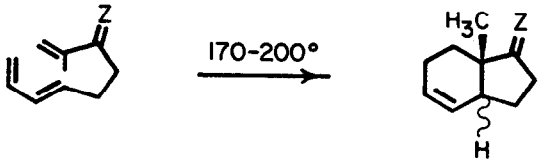
Scheme 1



1 2

Diels-Alder closure[6] (1 + 2). Indeed, both Jung[7] and Helquist[8] have independently proposed this approach, and have addressed the construction of the trans-hydrindenone via an intramolecular Diels-Alder reaction, Scheme 2. Unfortunately, only moderate selectivities (70-80% trans) were observed in the formation of protected hydrindenones.[9] In this paper we wish to report a

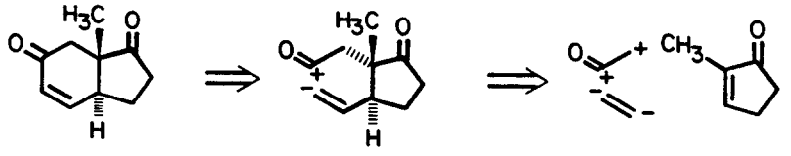
Scheme 2



stereoselective synthesis of the title compound 1.

Our approach (outlined in Scheme 3) relies on the well-documented preference[10] for a trans orientation of substituents derived from conjugate addition/trapping sequence with 2-methyl-2-

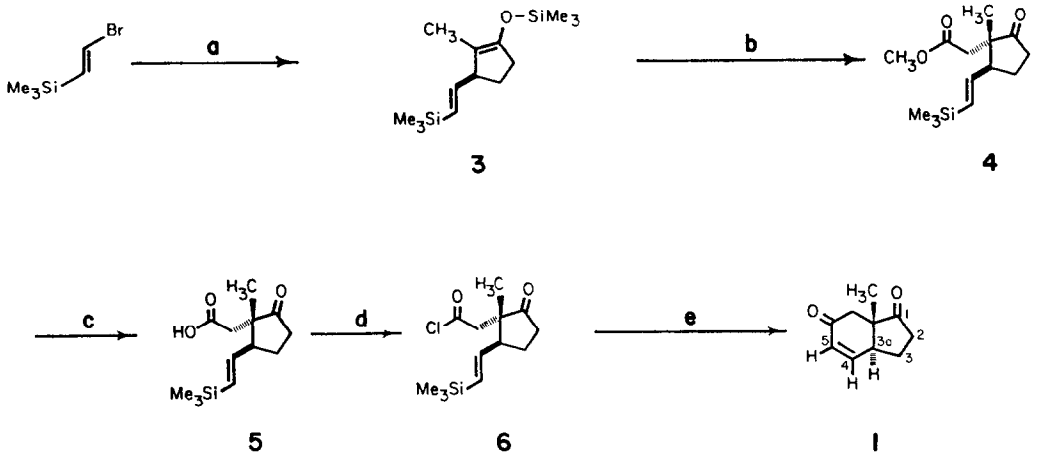
Scheme 3



cyclopentenone. The only modification needed was the incorporation of a vinyl-α,β-dianion synthetic equivalent in the conjugate addition. We selected the 2-trimethylsilylvinyl cuprate since the ability of vinylsilanes to promote and direct acylations[11] and especially cyclizations[12] has been amply demonstrated.

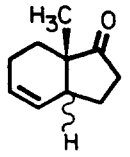
The synthetic sequence is detailed in Scheme 4. Treatment of 2-methyl-2-cyclopentenone[13] with the cuprate derived from E-2-trimethylsilylvinylmagnesium bromide[14] in THF at -70°C resulted in clean 1,4-addition[15a] within 15 minutes. Quenching of the enolate with TMSCl, Et_3N and HMPA at -70°C was complete within 10 minutes.[15b] Extractive workup (pentane/H_2O) and distillation afforded a 78% yield of 3[16] (bp 95-98°C, 1.5 torr). A solution of the lithium enolate derived from 3 (CH_3Li, Et_2O, r.t., 30 minutes) as added[17] to an excess of methyl bromoacetate (5 eq) and HMPA (4 eq) in THF (-20°C, 20 minutes then r.t., 2 h). Extractive workup, removal of excess $BrCH_2CO_2Me$ by distillation and flash chromatography of the residue (silica gel, EtOAc/hexane 1:4) yielded 4[16] in 87% yield (trans/cis 95:5).[15b,18] Saponification of 4 with aq.-methanolic KOH afforded acid 5[16] in 65% yield after recrystallization from hexane[19] (mp 93-95°C). The acid chloride 6[20] ($(COCl)_2$, C_6H_6, r.t., 3 h) was not isolated but directly treated (after evaporation at C_6H_6 in vacuo and redissolution in CH_2Cl_2) with $AlCl_3$ (3.5 eq) to induce the cyclization. Purification of the crude product by flash chromatography (silica gel, EtOAc/hexane 1:1) and distillation afforded the target 1[16] in 54% yield (bp 100°C, 10^{-3} torr).

Scheme 4



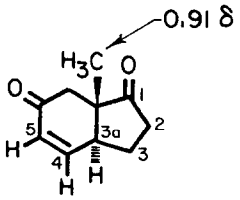
Reagents for Scheme 4: (a) (1) Mg, THF, reflux, 1.75 h; (2) CuI; (3) cool to -70°C, 2-methyl-2-cyclopentenone, THF, 30 min; (4) TMSCl, Et_3N, HMPA, -70°C to r.t., 2 h; (b) (1) CH_3Li, Et_2O-THF, r.t., 30 min; (2) inverse addition to $BrCH_2CO_2Me$ (5 eq), THF-HMPA (4 eq), -20°C → r.t., 12 h; (c) KOH, aq. CH_3OH, r.t., 20 h; (d) $(COCl)_2$, C_6H_6, r.t., 3 h; (e) $AlCl_3$ (4.5 eq), CH_2Cl_2, -30°C → r.t., 2 h.

The gross structure of 1 is evident from the characteristic olefinic region of the ^{1}H-NMR spectrum which displays a doublet of doublets at 6.93 δ (J = 10 and 2 Hz) for the H-C(5) and a doublet of doublets at 6.05 δ (J = 10 and 1 Hz) for H-C(4). The trans stereochemistry of the ring fusion is supported by ample precedent in the conjugate addition[10] as well as the similarity of the chemical shift for the angular methyl group in the trans isomer 7[7,8,9,21] (δ CH_3 (1), 0.91 ppm). The results of Diels-Alder reactions of 1 with 2 will be reported in due course.



7

	δ CH_3-C(7a)
trans	0.89
cis	1.04



Acknowledgement is made to the donors of the Petroleum Research Fund administered by the American Chemical Society for partial support of this research.

References and Notes

(1) Briggs, M. H.; Brotherton, J. "Steroid Biochemistry and Pharmacology"; Academic Press: New York, 1970; Ch. 6.

(2) For an excellent survey see: Blickenstaff, R. T.; Ghosh, A.-C.; Wolf, G. C. "Total Synthesis of Steroids"; Academic Press: New York, 1974.

(3) Johnson, R. A. in "Oxidation in Organic Chemistry, Part C"; Trahanovsky, W. S., Ed.; Academic Press: New York, 1978; Ch. 2.

(4) (a) Stork, G.; Logush, E. W. J. Am. Chem. Soc. 1980, 102, 1218.
(b) Stork, G.; Winkler, J. D.; Shiner, C. S. ibid. 1982, 104, 3767.
(c) Stork, G.; Shiner, C. S. ibid, 1981, 103, 4948.

(5) (a) Stork, G.; Shiner, C. S.; Winkler, J. D. J. Am. Chem. Soc. 1982, 104, 310.
(b) Stork, G.; Sherman, D. H. ibid. 1982, 104, 3758.
(c) Stork, G.; Winkler, J. D.; Saccomano, N. A. Tetrahedron Lett. 1983, 465.

(6) The intermediate shown is the product of an endo Diels-Alder transition state geometry.

(7) Jung, M. E.; Halmeg, K. M. Tetrahedron Lett. 1981, 3929.

(8) Helquist, P.; Bal, S. Tetrahedron Lett. 1981, 3933.

(9) For a thorough investigation of the stereochemistry in this and related cyclizations see: Roush, W. R.; Pesckis, S. M. J. Am. Chem. Soc. 1981, 103, 6696; and references cited therein.

(10) (a) Review: Funk, R. L.; Vollhardt, K. P. C. Chem. Soc. Rev. 1980, 9, 41. (b) Semmelhack, M. F.; Yamashita, A.; Tomesch, J. C.; Hirotsu, K. J. Am. Chem. Soc. 1978, 100, 5565.
(c) Oppolzer, W.; Battig, K.; Petrizilka, M. Helv. Chim. Acta 1978, 61, 1945.

(11) (a) Chan, T. H.; Fleming, I. Synthesis 1979, 761. (b) Colvin, E. "Silicon in Organic Synthesis"; Butterworths: Boston, 1981; Ch. 7.

(12) (a) Burke, S. D.; Murtishaw, C. W.; Pike, M. S.; Strickland, S. M. S.; Saunders, J. O. J. Org. Chem. 1981, 46, 2400. (b) Trost, B. M.; Maruyama, E. J. Am. Chem. Soc. 1981, 103, 6529. (c) Overman, L. E.; Bell, K. L. ibid. 1982, 104, 1851.

(13) Gassman, P. G.; Pascone, T. J. Am. Chem. Soc. 1973, 95, 7801.

(14) We employed the Grignard reagent as all attempts at bromine lithium exchange failed, c.f., Bruza, K. J.; Boeckman, R. K. J. Org. Chem. 1979, 44, 4781. The bromide was prepared according to: Mironov, V. F.; Petrov, A. D.; Maksimova, N. G. Zh. Ob. Khim. 1958, 1864.

(15) (a) GC analysis 11% QF-1 on 60-80 chromosorb G 1/8" x 6'. (b) GC analysis 20 m OV-101 capillary.

(16) Satisfactory ^{1}H NMR (90 or 220 MHz), IR, mass spectra, and combustion data were obtained for this compound.

(17) Inverse addition was essential for a high trans/cis ratio, c.f., references 10b, 10c.

(18) The assignment of stereochemistry is inferred from conversion to 1.

(19) The compound is very soluble in hexane and large material losses were incurred in purification. The crystalline nature of this compound is remarkable.

(20) IR ($CHCl_3$) 1800, 1740 cm^{-1}.

(21) Snider, B. B.; Kirk, T. C. J. Am. Chem. Soc. 1983, 105, 2364.

(Received in USA 31 March 1983)