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CHIRAL TRANS HYDRINDENONES : SYNTHESIS OF OPTICALLY PURE [3aαH(S), 7aβMe(S)]-TRANS-1-METHYL-7a-METHYLHYDRINDAN-1,4-DIENE-6-ONE.

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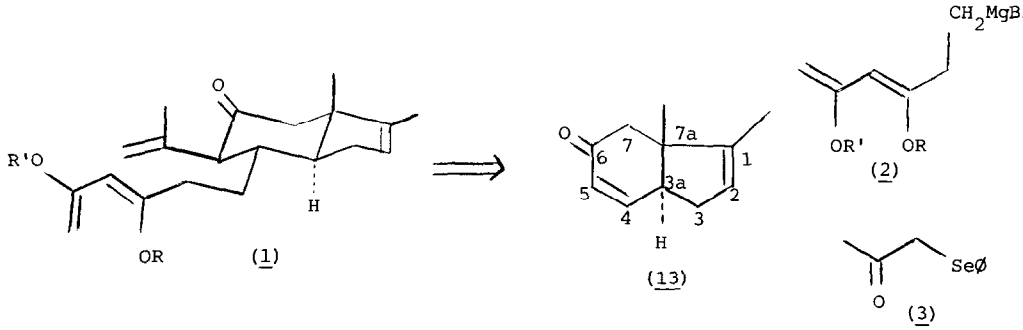
Summary: An intramolecular S_N2 displacement at an essentially neopentylic centre, capable of generating trans-hydrindenone (13) is described.

Trans hydrindenones[1] are of established value in the total synthesis of steroids[2,3,4]. Because of the paramount importance of steroids in medicine, several new methods for the synthesis of trans-hydrindenones have recently appeared. The focal point of these investigations has been to generate the crucial trans relationship of vicinal carbons (C-13 β-Me and C-14 α-H; steroid numbering) by utilizing (i) intramolecular Diels-Alder reaction,[5] (ii) intramolecular Michael reaction,[6] (iii) Lewis-acid catalyzed cyclization of γ,δ-unsaturated carbonyl derivatives,[7] (iv) Claisen rearrangement[8] and (v) the bicycloheptane fragmentation approach.[9]

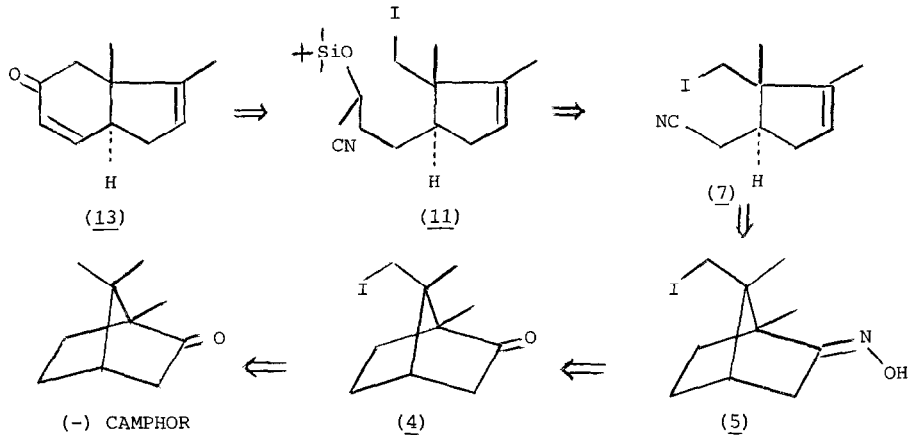
In order to test the viability of an intramolecular Diels-Alder reaction of optically pure (1), as a route to 11-keto steroids, e.g., (+) cortisone, we became interested in the synthesis of chiral trans-hydrindenone (13). Optically pure (1) itself, can be expected to arise via



Cu^+-catalyzed 1,4-conjugate addition of the Grignard reagent 2 to 13, followed by trapping[10] of the resulting enolate with (phenylseleno) acetone (3).

Our retrosynthetic plan for the synthesis of the chiral trans-hydrindenone (13) is shown in Scheme 1. We were attracted to this possibility because of the following considerations: (i) In analogy with the observation of Stevens and Gaeta,[9] we expected that a highly functionalized chiral cyclopentene (7), having the correct trans relationship at the vicinal carbons (C-13 β-Me and C-14 α-H) would be readily available by the 2nd-order Beckmann fragmentation

Scheme 1



from the anti-oxime of (-) π-iodocamphor (4), and (ii) that it provided for the opportunity to examine a novel annelation sequence[11] involving intramolecular S_N2 displacement at an essentially neopentylic centre by an acyl anion equivalent, derived from a protected cyanohydrin (e.g. 11 ↛13). This has now been accomplished and the results discussed below are noted in order to underline the importance of this work towards the enantiomer synthesis of trans-hydrindenone (13). The successful route that was employed is shown in Fig. 1.

Oximination of the (-) π-iodocamphor (4),[9] m.p. 61-63°C, $[\alpha]_D$ -173.4° (c, 0.47%)[12] gave the anti-oxime (5), m.p. 121-123°C, $[\alpha]_D$ -11.5° (c, 0.54%) in quantitative yields. On treatment of 5 with TsCl in pyridine at 0°C, it underwent "second-order" Beckmann rearrangement to give approx. 1:1 mixture of cyclopentenes (6 and 7). Equilibration of this mixture with anhydrous CF_3COOH in CH_2Cl_2 furnished in 81% yields (from 5) pure 7 $[\alpha]_D$ -23.1° (c, 0.58%); ^{1}H-NMR (100 MHz, $CDCl_3$, δ): 1.08 (s, 3H, CH_3-C), 1.64 (br s, CH_3C=CH), 2.0-2.8 (m, 5H, NC-CH_2-CH-CH_2-CH=C), 3.22 and 3.36 (pair of doublets, J_{ab} = 12 Hz, ICH_2-C-), 5.4 (br s, 1H, CH_3C=CH-CH_2). Reduction of the nitrile function in 7 with neat $(i\text{-Bu})_2$AlH under Nitrogen in 1:1 dry toluene-hexane mixture, followed by aq. acid hydrolysis gave in 95% yield the aldehyde 8, $[\alpha]_D$ -11.64° (c, 0.45%), IR (Neat): C=O, 1720 cm^{-1}. ^{1}H-NMR (100 MHz, $CDCl_3$, δ): 9.65 (t, J = 1.5 Hz, 1H, -CH_2CH=O). One carbon homologation of the aldehyde (8) was accomplished by the Horner-Wittig reaction as developed by Warren and coworkers,[13] except that the hydrolysis of the derived enol ether (9) was performed using[14] 20% oxalic acid in refluxing THF. Thus aldehyde (10), m.p. 33.0-33.5°C, $[\alpha]_D$ -4.12° (c, 0.48%); IR (Neat) C=O 1720 cm^{-1}; ^{1}H-NMR (100 MHz, $CDCl_3$, δ): 9.85 (t, J = 1.5 Hz, 1H, -CH_2-CH=O) was obtained in 92% isolated yields. The derived (over 95% yield) cyanohydrin tert-butyldimethylsilylenol ether (11) was cyclized[15] under argon as follows:

The protected cyanohydrin (11, 216.5 mg, 0.5 mmole) taken in 2 ml of dry THF was introduced dropwise at -45°C to the freshly prepared LDA (0.75 mmole) in THF (2 ml) containing HMPA (130 µl). After stirring for 15 minutes, the reaction mixture was quenched with H_2O, and extracted in ether, the crude cyclized product (∿150 mg) was stirred with a solution of

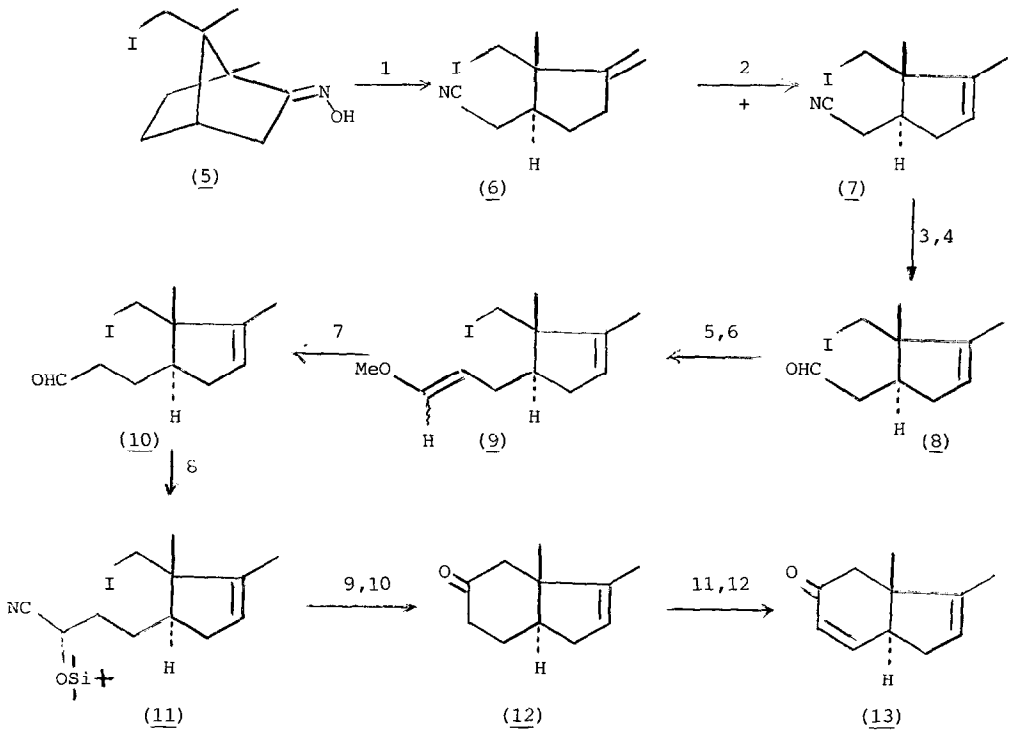


Fig. 1. SYNTHESIS OF TRANS-HYDRINDENONE (13):

(1) TsCl (1.1 equ.), Pyridine, 0°, 20 hrs.; (2) CF_2COOH. (4 equ.) - CH_2Cl_2, 12 hrs; (3) $(i\text{-Bu})_2AlH$ (1.1 equ.), -5°C, hexane-toluene (1:1); (4) 2N HCl; (5) $\emptyset_2P(O)CH_2OMe$ and LDA (1.1 equ.) - THF, -78°C; (6) KH-THF; (7) 20% $(COOH)_2$ - THF, reflux, 4 hrs; (8) $(CH_3)_3Si$-CN/KCN-18-Crown-6; $H_3\overset{+}{O}$; t-$BuMe_2SiCl$ - DMF and imidazole; (9) LDA (1.5 equ.) - THF, HMPA (2 equ.), -45°C, 15 min; (10) $(n\text{-Bu})_4\overset{+}{N}F^{\theta}$ - THF; (11) LDA (1.1 equ.) - THF, -78°C, ØSeCl (1.1 equ.); (12) 30% H_2O_2-CH_2Cl_2 (containing a drop of pyridine).

$n\text{-Bu}_4\overset{+}{N}F^{\theta}$ (1M in THF, 1 ml) in 3 ml of dry THF for 30 minutes. After usual work up and purification by flash chromatography, 54.0 mg (65% yield) of pure 12, $[\alpha]_D$ + 135.1° (c, 0.33%); IR (Neat) C=O 1710 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$ δ): 0.71 (d, J = 0.88 Hz, 3H, $C\underline{H}_3$C-CH), 1.63 (br s, 3H, $C\underline{H}_3$C=CH), 1.85-2.05 (m, 3H, $-CH_2C\underline{H}_2-C\underline{H}-CH_2-$), 2.12-2.55 (m, having a distinct pair of doublets. J = 13.5 Hz, 6H, C-$C\underline{H}_2$-CO-$C\underline{H}_2$-CH_2 and C=CH-$C\underline{H}_2$-CH), 5.37 (br s, 1H, $CH_3C=C\underline{H}-CH_2$). Mass: m/e 164.1 $C_{11}H_{16}O$. (M^+, 42.46%), 149.1 (M^+-CH_3, 100%), was obtained.

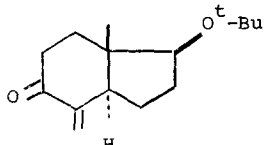
Introduction of the double bond adjacent to the carbonyl function in 12 was accomplished[16] by first preparing the α-selenoketone, followed by the fragmentation of its selenoxide to give in 90% yields the trans-hydrindenone (13), $[\alpha]_D$ +205.3 (c, 0.18%); IR (Neat): C=C-C=O 1675 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 0.80 (d, J = 0.85 Hz, 3H, $C\underline{H}_3$C-CH), 1.65 (br s, 3H,

$CH_3C=CH-$), 2.0-2.21 (m, 2H, $CH-CH_2-CH=CCH_3$), 2.30 and 2.60 (pair of doublets. J_{ab} = 15 Hz, 2H, $COCH_2-C-$), 2.91 (m, 1H, $HC=CH-CH-CH_2-$); 5.4 (br s, 1H, $CH_3C=CH-CH_2$): 6.0 (dd, J = 15 Hz and 3 Hz, 1H, $O=C-CH=CH-CH$); 7.1 (dd, J = 15 Hz, and 3 Hz, 1H, $O=C-CH=CH-CH$); Mass: m/e 162.1 $C_{11}H_{14}O$ (M^+, 58.3%), 147.1 (M^+-CH_3; 100%).

The efficiency of the intramolecular S_N2 process disclosed in this Letter is appealing and we believe that it should find several applications in the construction of complex natural products.[17]

REFERENCES AND NOTES

1. Such as (i) to (iii)



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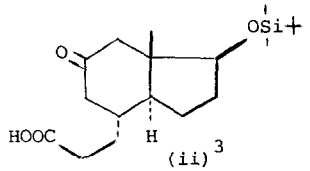

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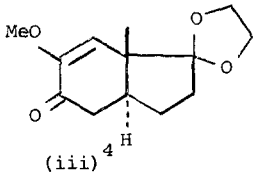

(iii) 4

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