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BORON ANNULATION: TOTAL SYNTHESIS OF (±)-ESTRONE METHYL ETHER

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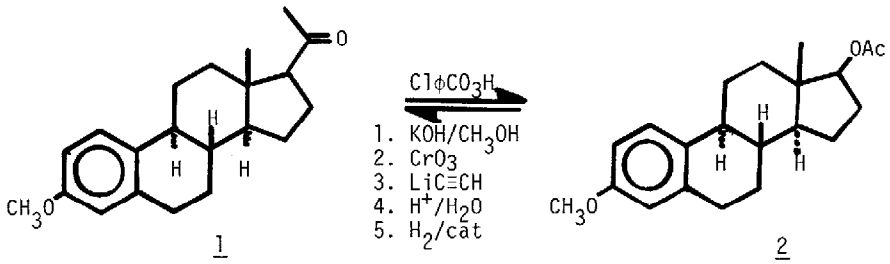
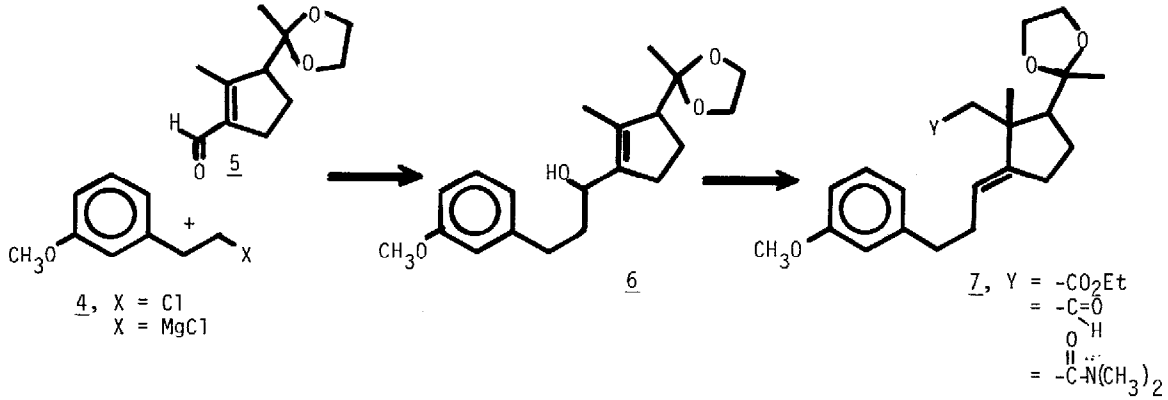
SUMMARY: The stereoselective hydroboration and carbonylation of highly functionalized 1,4-dienes affords trans-hydrindanones in good yield. These trans-hydrindanones are synthons for norpregnenolone, estrone and related estradiol derivatives.

In evaluating the Brown hydroboration-carbonylation[1] procedure as a versatile technique for Natural Products synthesis, we have prepared norpregnenolone (1) to test not only the regio- and stereochemical control of stitching and riveting but also the functional group tolerances of these reactions. We chose this target steroidal system since it has been degraded to estradiol derivatives[10] (i.e. 2) and/or the C-17 acetyl group could be elaborated to other naturally occurring steroid side chain units.[3]

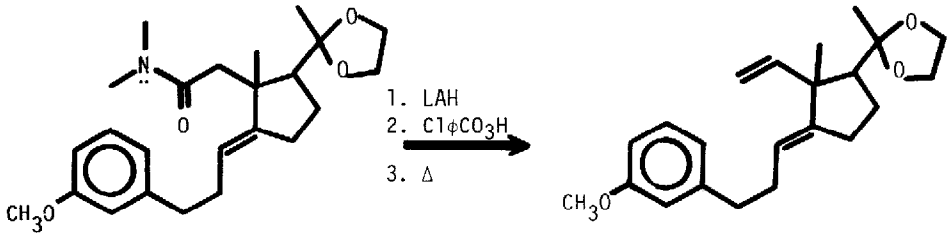


1 2

To conduct this test diene 3 was prepared in a convergent manner by the addition of the Grignard reagent of m-methoxyphenethyl chloride (4) to ketal carboxaldehyde 5 yielding alcohol 6 [78%; $\lambda_{cm^{-1}}^{film}$, 3410 (OH), 1605 (Ar); $\delta_{CDCl_3}^{TMS}$, 1.7 (s, allylic methyl hydrogens), 4.55 (t, allylic methine next to oxygen); m/e, 332].[4]

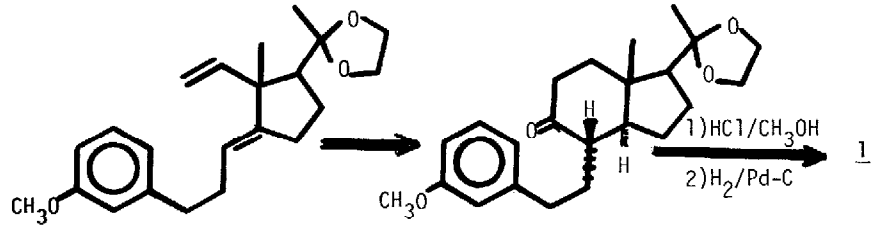


Claisen rearrangement of 6 using ortho ester or vinyl ether techniques were only partially successful in forming 7 (Y = $-CO_2Et$ or $-\overset{O}{\overset{\|}{C}}-H$) due presumably to steric restraints present in the allylic alcohol 6 which is a mixture of diastereomers.[13] However, acetamide acetal[6] rearrangement in refluxing xylene with 6 readily afforded amide 7 [Y = $Me_2N-\overset{O}{\overset{\|}{C}}-$; 83%; $\lambda^{film}_{cm^{-1}}$ 1650 (CO); $\delta^{TMS}_{CDCl_3}$, 5.0 (m, vinyl H), 2.85 and 2.88 (N,N-dimethyl), 0.9 and 1.1 (two s, angular methyl groups);[11] m/e = 401] which, in turn, was reduced to amine 8 [($LiAlH_4$ in Et_2O, 88%; $\lambda^{film}_{cm^{-1}}$, 1605; $\delta^{TMS}_{CDCl_3}$, 2.1 (N,N-dimethyl)]. The N-oxide of 8, (9), was formed with m-chloroperbenzoic acid[9; 85%; $\lambda^{film}_{cm^{-1}}$, 1605, 1045, 945; $\delta^{TMS}_{CDCl_3}$, 3.0 (s, N,N-dimethyl)]. Cope elimination[14] of 9 by heating (135°C) under vacuum (0.1 mm Hg)[3] afforded the target 1,4-diene 3 [60% $\lambda^{film}_{cm^{-1}}$, 3075, 1630, 1600; $\lambda^{TMS}_{CDCl_3}$, 6.1-4.85 (4 vinyl H's), 1.25 and 1.05 (s, angular methyls)].[11]



7 3

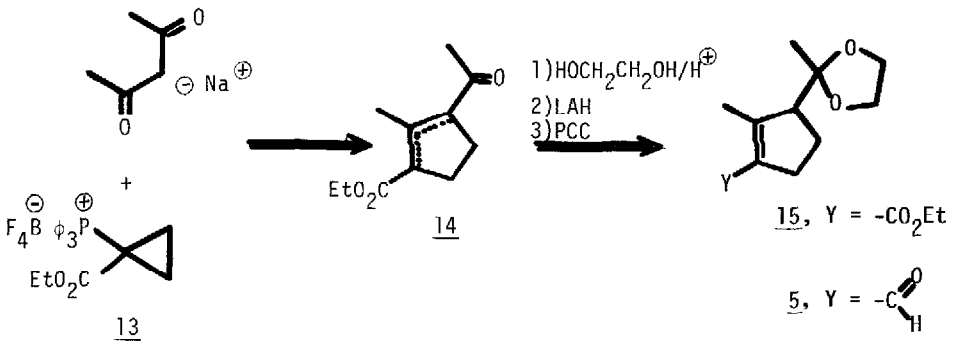
Hydroboration [(thexylborane from $H_3B{\cdot}S(CH_3)_2$ and 2,3-dimethyl-2-butene in THF, 0°, 15 h)] of diene 3 followed by carbonylation (KCN, TFAA, then H_2O_2)[7] gave hydrindanone 12 [60%; $\lambda^{film}_{cm^{-1}}$, 1710, 1605 $\delta^{TMS}_{CDCl_3}$, 1.1 and 0.9 (singlets, angular methyl groups); m/e, 372] with the desired relative stereochemistry as anticipated from previous model studies.[8] Standard procedures[9] form 1 from 12 in two steps [HCl/MeOH, then H_2/PdC, 60%; mp 128-130 (lit.133)[15]; $\lambda^{film}_{cm^{-1}}$, 1715, 1605; $\delta^{TMS}_{CDCl_3}$, 0.75 and 1.00 (angular methyl group)].[11] This ketone was roughly a 3 to 1 mixture of the β to α C-17 epimers which proved identical spectroscopically to the C-17



3 12 1

epimeric mixture of 1 prepared by published procedures[2,15] from estradiol. Baeyer-Villiger oxidation of 1 (to 2, m-chloroperbenzoic in CH_2Cl_2),[10] hydrolysis (10% KOH/methanol) and oxidation (Jones reagent) provides estrone methyl ether.

The D-ring synthon 5 was prepared using the method of Fuchs.[12] The addition of sodio acetylacetone to carbethoxycyclopropylphosphonium tetrafluoroborate (13) yielded keto ester 14 (90%, bp 90-95° @ 1 mm Hg) as a mixture of double bond isomers.[16] Ketalization (ethyleneglycol, toluene, p-toluenesulfonic acid) gave ester 15 [80%; bp 100-105° @ 5 mm Hg $\lambda^{film}_{cm^{-1}}$, 1705; $\delta^{TMS}_{CDCl_3}$, 2.2 (s, vinyl methyl)] which was, in turn, converted to aldehyde 5 by reduction ($LiAlH_4$ in ether, 80%; bp 88-90° @ 0.9 mm Hg; $\lambda^{film}_{cm^{-1}}$, 3390) and PCC oxidation [62%; $\lambda^{film}_{cm^{-1}}$, 2750, 1665; $\delta^{TMS}_{CDCl_3}$, 10.2 (aldehyde-H), 2.15 (vinyl methyl group)].



13 14 15, Y = $-CO_2Et$ 5, Y = $-C(=O)H$

Clearly, the strategy of stitching and riveting is compatible with synthesis of a wide range of sterically demanding, functionalized natural products. We are currently pursuing more complex target systems, as well as investigating more direct routes to the olefinic synthons to be used for estrone and progesterone total synthesis.

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3. For a recent example of C_{17} side chain construction see: M. Tanabe and K. Hayashi, J. Amer. Chem. Soc., 102, 862 (1980).
4. All compounds exhibited the anticipated ir, pmr, cmr, uv and mass spectra. Compounds 3 and 1 gave satisfactory CH analysis.

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11. The C_{17} acetyl group is an epimeric mixture. This results in two resonances for the C_{13} methyl groups. The only rearranged structure that does not exhibit this resonance doubling of the C_{13} methyl group is ortho ester product 7 (Y = CO_2Et), see footnote 13.
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13. Triethylorthoacetate Claisen rearrangement of 6 resulted in about 50% of the desired rearrangement product and ~50% of recovered starting material, alcohol 6 (following hydrolysis of the acetate). Further attempts at rearrangement with this material were fruitless suggesting that the epimeric, ketalized acetyl group of alcohol 6 creates hindered and less hindered diastereomeric pairs of intermediates for Claisen rearrangements and that the recycled material probably has the syn relationship between the alcohol group and the ketalized acetyl side chain.
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16. CMR of keto ester 14 exhibits resonance doubling which disappears on ketalization to ester 15.

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