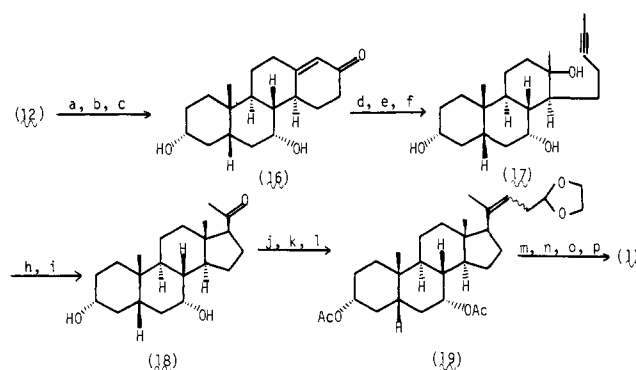
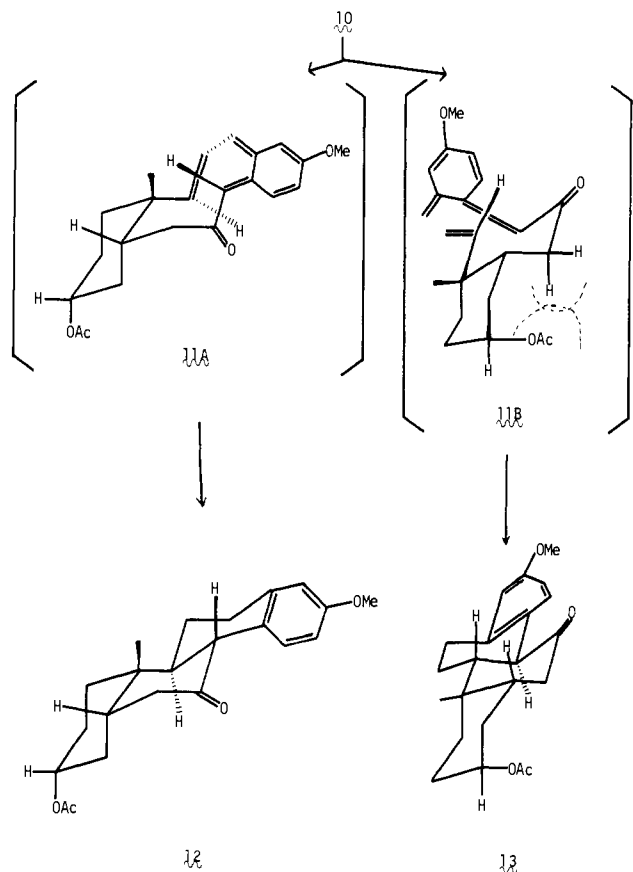


Scheme II^a

^a (a) LiAlH_4 , THF, room temperature; (b) Li, liq NH_3 , *t*-BuOH, -78°C ; (c) 10% HCl, MeOH, reflux; (d) 30% H_2O_2 , 10% NaOH, MeOH, room temperature; (e) *p*-TsNHNH₂, AcOH, CH_2Cl_2 , 15 h at -18°C , then 4 h at room temperature; (f) MeLi, THF, 0°C ; (g) MeI, LiNH₂, liq NH_3 , THF, -33°C ; (h) $\text{CF}_3\text{CO}_2\text{H}$, $(\text{CF}_3\text{CO})_2\text{O}$, room temperature; (i) 10% KOH, MeOH, room temperature; (j) 3,3-(ethylenedioxy)propylmagnesium bromide, THF, room temperature; (k) Ac₂O, 4-(dimethylamino)pyridine, pyridine, room temperature; (l) POCl_3 , pyridine, room temperature; (m) H_2 , Pt, MeOH, room temperature; (n) 10% HCl, acetone, room temperature; (o) Jones' reagent, acetone, 0°C ; (p) 10% NaOH, MeOH, reflux.

of sterically favored transition state **11a** rather than **11b** which has steric repulsion between acetoxy and methylene groups, giving the cis, syn, trans-compound **13**.

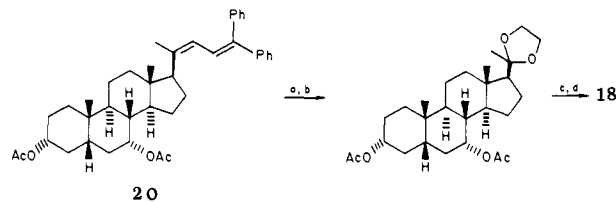


With cis,anti,trans-D-ring aromatic steroid **12** in hand, conversion to chenodeoxycholic acid (**1**) requires D-ring manipulation and introduction of substituents stereoselectively (Scheme II).^{9,14} The enone **16**, prepared in 35% overall yield from **12**, was converted into acetylenic alcohol **17** in 30.7% overall yield, including Eschenmoser ring-opening reaction of epoxy ketone. Acid-catalyzed ring closure of **17** was carried out in a stereoselective manner to give the pregnane-type steroid **18** in 80.5% overall yield.¹⁰ The

20(22)-dehydro compound **19** derived in 22% overall yield from **18** via Grignard reaction with 3,3-(ethylenedioxy)propylmagnesium bromide prepared from the corresponding bromide¹² followed by dehydration¹³ was converted into chenodeoxycholic acid (**1**) in 33.2% overall yield. The synthetic substance was found to be identical with natural chenodeoxycholic acid in all aspects, including IR (CHCl_3), NMR (CDCl_3), mass spectra, and optical rotation, as well as mixed melting point.

Thus we could accomplish first total synthesis of (+)-chenodeoxycholic acid (**1**). Since chenodeoxycholic acid (**1**) has been transformed¹⁵ into ursodeoxycholic acid (**2**), this work also constitutes the formal total synthesis of ursodeoxycholic acid (**2**). This synthetic methodology could be applied for the synthesis of a wide range of cis, anti, trans-fused steroidal compounds.

(10) At this stage, in order to confirm the structure including the stereochemistry of the chiral center of **18**, an alternative synthesis of **18** was carried out starting from **20**,¹¹ and the synthetic substance was identified with an authentic sample in its spectral (IR, NMR, MS) comparison.



Reagents: (a) O_3 , AcOEt, -78°C , then Me_2S ; (b) $\text{HOCH}_2\text{CH}_2\text{OH}$, *p*-TsOH, benzene, reflux; (c) LiAlH_4 , THF, room temperature; (d) 5% HCl, MeOH, room temperature. The optical purity of synthetic substance was calculated to be 93.2% by direct comparison with the authentic sample prepared as above.

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Transition State of Oxidative Addition Reaction: $\text{Pt}(\text{PH}_3)_2 + \text{H}_2 \rightarrow \text{Pt}(\text{H})_2(\text{PH}_3)_2$

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Recent studies on preparation and reactions of two-coordinate platinum(0)- [and palladium(0)-] phosphine complexes present an interesting chemistry of homogeneous catalytic activities.¹⁻³ Some of them easily absorb molecular hydrogens.¹ Some PtL_2 (L = chelating phosphine) species react reversibly with H_2 .² A suggestion has been made for controlling their reactivity with the interligand angle^{3,4} as well as the steric size and basicity of phosphine ligands.^{2,3} The identification of transition state along with equilibrium structures is one of the essential steps to better understanding of the mechanism of oxidative addition.

In this paper we present for the title reaction a transition state fully optimized in the ab initio method, a first such determination for a reaction involving transition-metal complexes. The transition state, leading to the cis adduct with a low barrier, is an early

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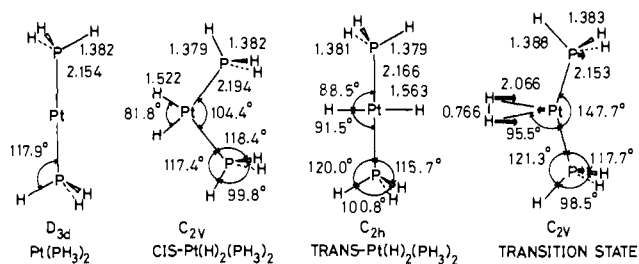


Figure 1. Fully optimized geometries (in Å and deg) of $\text{Pt}(\text{PH}_3)_2$, $\text{cis-Pt}(\text{H})_2(\text{PH}_3)_2$, $\text{trans-Pt}(\text{H})_2(\text{PH}_3)_2$, and the transition state. Arrows in the transition state show the reaction coordinate vector.

Table I. Calculated Energy Profile Relative to $\text{Pt}(\text{PH}_3)_2 + \text{H}_2$ (in kcal/mol)

method	transition state	<i>cis</i> - $\text{Pt}(\text{H})_2$ - $(\text{PH}_3)_2$	<i>trans</i> - $\text{Pt}(\text{H})_2$ - $(\text{PH}_3)_2$
RHF	+5.2	-36.9	-38.0
CI	+8.7	-27.0	-25.1
CI + QC ^a	+7.1	-27.0	-24.2
CI + QC + ZPC ^a	+8.2	-21.7	-20.5

^a QC, correction for unlinked quadruple excitations (Davidson, E. R.; Silver, E. W. *Chem. Phys. Lett.* 1977, 52, 403). ZPC, correction for zero-point energy.

transition state where the HH bond is stretched only 4%.

Calculations were performed for a singlet, the ground state according to experimental evidences.¹⁻³ We optimized all the degrees of freedom by using the energy gradient⁵ at the restricted Hartree-Fock (RHF) level under the relativistic effective core potential approximation.⁶ A smaller basis set (valence double except for the PH_3 part)⁷ was used for calculating structures and normal modes and a larger set (all valence double)⁷ for energies. To obtain better energetics, configuration interaction (CI) calculations were carried out at RHF optimized geometries with the larger basis set, including all the single and double excitations relative to the RHF configuration (about 67 000 configurations in C_2).¹⁰

The calculated geometries and energies of the reactant, products, and transition state are shown in Figure 1 and Table I. The transition state has the C_{2v} symmetry, and its reaction coordinate, the only normal coordinate with an imaginary frequency, shown by the arrows in Figure 1, consists mainly of the H_2 relative motion and the PPtP bending motion. It leads to the cis product. The PPtP angle is bent about 30° from that (180°) of the reactant. The HH bond is only 4% longer than that of the free H_2 . The transition state is in an early stage of reaction, a reasonable finding for an exothermic reaction. In a kinetic study of another H_2 addition reaction $\text{IrCl}(\text{CO})(\text{PPh}_3)_2 + \text{H}_2$, it has been suggested that the HH bond stretching is small at the transition state.¹¹

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The transition state yielding directly the trans product was not found. A "transition state", found with the H_2 axis kept perpendicular to the PPtP plane, belongs to the C_{2v} symmetry and has two normal modes of imaginary frequency, one leading downhill to the trans product and the other through an H_2 rotation to the reaction path for the cis product. This is not surprising, because the trans addition to ML_2 with d^{10} configuration is symmetry forbidden.¹² It is likely, therefore, that the reaction proceeds first via cis addition, which could be followed by the isomerization to the trans product through one of suggested paths¹³ such as a five-coordinate complex involving a solvent molecule.

Our best calculation (CI + QC) gives a barrier height of 7 kcal/mol for the cis addition. The zero-point energy correction (ZPC) based on the RHF calculated force constants changes the effective barrier to 8 kcal/mol. Though these values should be taken to be only semiquantitative, it is safe to say that the barrier for this model reaction is low, consistent with the experimental fact that oxidative addition reactions usually take place easily.

The geometries of the reactant and the products in the smaller basis set in Figure 1 compare favorably with those in the larger set as well as known experimental results of related compounds.⁵ The energy difference between *cis*- and *trans*- $\text{Pt}(\text{H})_2(\text{PH}_3)_2$ is within a few kilocalories per mole for all the methods in Table I and is certainly below the reliability of the present calculation. Most of the experimentally known diphosphine Pt(0) complexes have bulky phosphines as ligands.¹ Bulky phosphines probably will raise the barrier by destabilizing the transition state. The steric destabilization is probably even more serious in the cis product because of a smaller PPtP angle (104°). This may account for the reason why only trans products have been isolated, except for cis products of chelating phosphines where the isomerization path is obviously closed.²

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Chemical Modification of Deoxyribonucleic Acids: A Direct Study by NMR Spectroscopy

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Chemical modification of biological macromolecules,¹⁻⁴ particularly polynucleotides,^{1,5-12} is one of the promising approaches for studying the structure and function of biopolymers and bioactive substances.¹³⁻¹⁵ It is evident that the success of this

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