their Mössbauer data of Lithium (iron) 4,5-(phthalocyanin)-tetrahydrofuran as indicative of a d^6 rather than d^7 iron. The NMR spectrum of **6b** was identical with that shown in Figure 1.

When the hydrolysis product at pH 9.5 was aerated for 1 min, the peaks at $g = 2.30$ and 1.76 disappeared (Figure 2D') with concomitant formation of ferrous low-spin verdohemochrome in a high yield. Thus the verdohemochrome formation from iron oxymesoporphyrin involves oxidation of Fe(I) to Fe(II) by molecular oxygen. This conclusion was also supported by the NMR and Mössbauer data. However, when the supply of oxygen was limited to a trace amount, the $g = 1.999$ signal appeared (Figure 2D), thus indicating the involvement of a free radical. Elucidation of the chemical nature of this radical ($O_2^{-}\cdot$ or porphyrin π radical) is currently under way.

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First Total Synthesis of (+)-Chenodeoxycholic Acid

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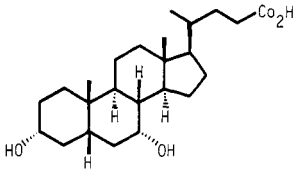
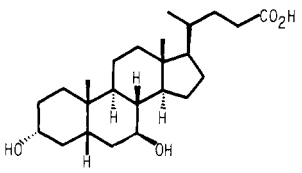
Chenodeoxycholic acid (**1**) is one of the two primary bile acids in man and recently has attracted much attention because of its clinical importance in the treatment of gallstones. Studies around the world, including countries where chenodeoxycholic acid (**1**) is now available for general medical use, have shown that about 60% of patients treated with chenodeoxycholic acid (**1**) have stone dissolution.[1-3] Ursodeoxycholic acid (**2**) has also been shown to



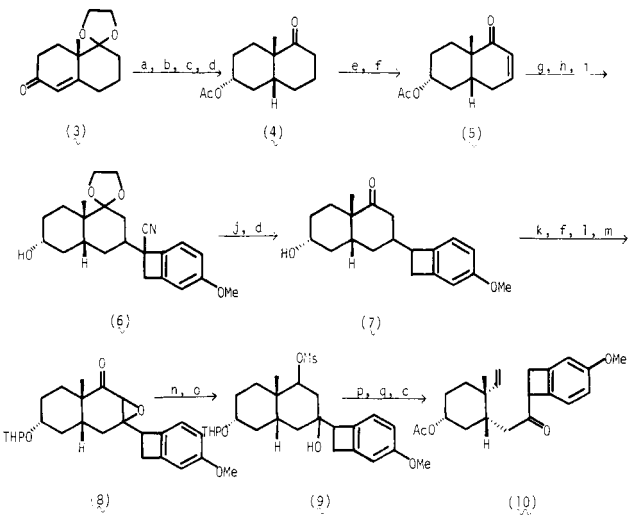
(1)



(2)

have almost the same activity as chenodeoxycholic acid for treatment of gallstones.[4] These facts and the difficulties of obtaining a pure sample of chenodeoxycholic acid (**1**) by separating structurally closely related concomitants which prevent accurate biological evaluation of **1** prompted us to report the first, highly stereoselective total synthesis of (+)-chenodeoxycholic acid (**1**) in an optically pure form. One of the key strategies for this synthesis involved the use of olefinic benzocyclobutene **10** which has an α-acetoxy group on the cyclohexane ring to direct the stereochemical course of intramolecular cycloaddition of *o*-quinodimethane **11a** derived from thermolysis of **10** to form cis, anti, trans-D aromatic steroid **12** stereoselectively.[5]

Scheme I[a]



[a] Reagents: (a) H_2, Pd–C, EtOH, room temperature; (b) $NaBH_4$, MeOH, 0 °C; (c) Ac_2O, pyridine, room temperature; (d) 10% HCl, acetone, room temperature; (e) Br_2, $CHCl_3$, room temperature; (f) LiBr, Li_2CO_3, DMF, 125 °C; (g) 1-cyano-4-methoxybenzocyclobutene, $NaNH_2$, liq NH_3, −78 °C; (h) $HOCH_2CH_2OH$, *p*-TsOH, C_6H_6, reflux; (i) 5% NaOH, MeOH, room temperature; (j) Na, liq NH_3, −78 °C; (k) pyridinium hydrobromide perbromide, $CHCl_3$, room temperature; (l) 30% H_2O_2, 10% NaOH, MeOH, room temperature; (m) dihydropyran, *p*-TsOH, CH_2Cl_2, room temperature; (n) $LiAlH_4$, THF, room temperature; (o) MsCl, pyridine, room temperature; (p) NaH, THF, reflux; (q) *p*-TsOH, room temperature.

The key intermediate, optically active [2-(benzocyclobutenyl)ethyl]cyclohexane **10**, was prepared from (8a*S*)-1,1-(1,2-ethylenedioxy)-1,2,3,4,6,7,8,8a-octahydro-8a-methyl-6-oxonaphthalene[6] (**3**) by the route shown in Scheme I.[14] The optically active *cis*-octalone **5**, readily prepared in 56.2% overall yield from **3**, was converted into benzocyclobutene **7** in 83.7% overall yield from **5**, including Michael addition of 1-cyano-4-methoxybenzocyclobutene[7] followed by reductive decyanation. The epoxide **8** derived in 73.5% overall yield from **7** in a usual manner was transformed into the key intermediate **10** in 52.2% overall yield from **8** via the fragmentation of hydroxy mesylate **9**. Thermolysis of **10** was conducted in boiling *o*-dichlorobenzene in a current of nitrogen for 45 min to afford cis, anti, trans-D aromatic steroid **12** stereoselectively in 42.7% yield.[8] This was the first observation that the thermolysis of olefinic benzocyclobutene which has ethenyl and (benzocyclobutenyl)ethyl groups in cis relationship gave cis, anti, trans-fused steroidal compound stereoselectively. This stereoselectivity could be reasonably explained by the intervention

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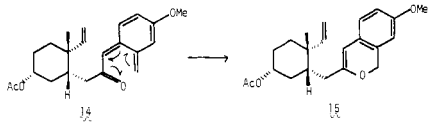
(8) Stereoisomers other than benzopyran (**15**; 20.4% yield) could not be obtained . The formation of **15** could be well understood by electrocyclic reaction of *o*-quinodimethane (**14**). In case of trans relationship between



ethenyl and (benzocyclobutenyl)ethyl groups, stereoselectivity of intramolecular cycloaddition reaction of *o*-quinodimethanes has been observed to give trans, anti, trans-fused steroidal compounds: (a) Kametani, T.; Suzuki, K.; Nemoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 1127. *J. Org. Chem.* **1980**, *45*, 2204.
(9) Transformation of D-ring aromatic steroids into pregnane-type steroids has been developed by us. See: (a) Kametani, T.; Suzuki, K.; Nemoto, H. *Tetrahedron Lett.* **1980**, 1469. (b) Kametani, T.; Suzuki, K.; Nemoto, H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2805. (c) Kametani, T.; Tsubuki, M.; Nemoto, H. *Tetrahedron Lett.* **1980**, 4855.

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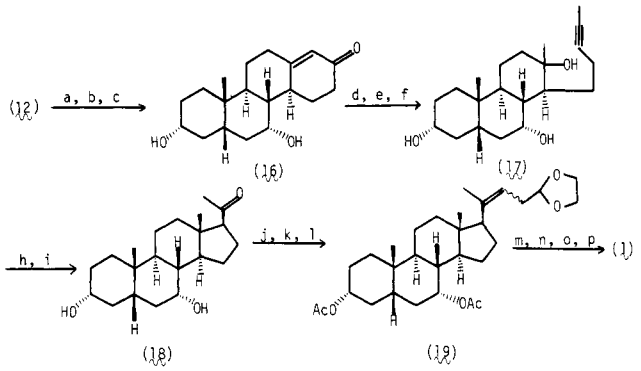
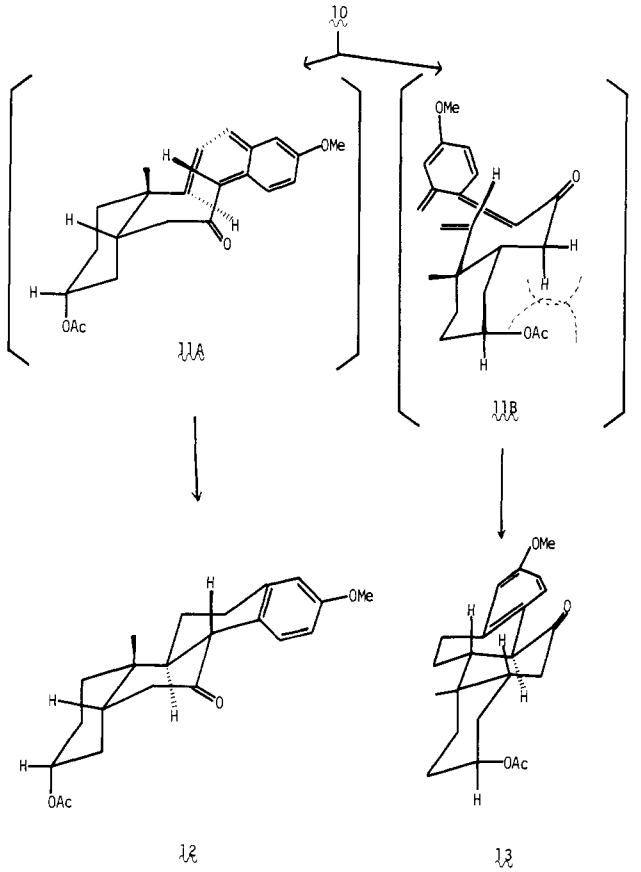
Scheme II[a]



[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*-TsNHNH$_2$, AcOH, CH_2Cl_2, 15 h at −18 °C, then 4 h at room temperature; (f) MeLi, THF, 0 °C; (g) MeI, $LiNH_2$, liq NH_3, THF, −33 °C; (h) CF_3CO_2H, $(CF_3CO)_2O$, room temperature; (i) 10% KOH, MeOH, room temperature; (j) 3,3-(ethylenedioxy)propylmagnesium bromide, THF, room temperature; (k) Ac_2O, 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.

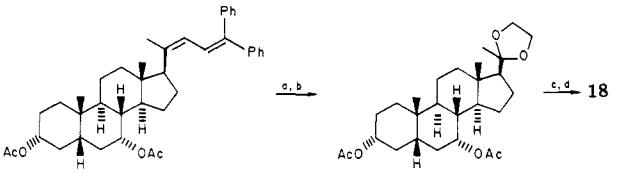
of sterically favored transition state **11a** rather than **11b** which has steric repulsion between acetoxy and methylene groups, giving the cis, syn, trans-compound **13**.



With cis,anti,trans-D-ring aromatic steroid **12** in hand, conversion to chenodeoxycholic acid (**1**) requires D-ring manipuration 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 bromide[12] followed by dehydration[13] 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 transformed[15] 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) $HOCH_2CH_2OH$, *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: $Pt(PH_3)_2 + H_2 \rightarrow Pt(H)_2(PH_3)_2$

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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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