The ^{19}F NMR spectra were obtained as described in the accompanying paper[10] for solutions (0.5 mL) containing the unsubstituted (X = H, 1 mg) and substituted (1 mg) compounds in the appropriate solvent.

Registry No. 1 (X = COF), 81725-03-3; 1 (X = NO_2), 32038-89-4; 1 (X = CN), 78385-80-5; 1 (X = CF_3), 78385-81-6; 1 (X = COOH), 78385-84-9; 1 (X = $CONH_2$), 81687-77-6; 1 (X = $COOCH_3$), 78385-85-0; 1 (X = $COCH_3$), 78385-83-8; 1 (X = CHO), 78385-82-7; 1 (X = OH), 22947-61-1; 1 (X = OCH_3), 78385-90-7; 1 (X = $OCOCH_3$), 22947-60-0; 1 (X = F), 20277-40-1; 1 (X = Cl), 78385-86-1; 1 (X = Br), 78385-87-2; 1 (X = I), 78385-89-4; 1 (X = NH_2), 78385-91-8; 1 (X = $N(CH_3)_2$), 78385-92-9; 1 (X = $NHCOCH_3$), 78385-93-0; 1 (X = $^+NH_3$), 81725-04-4; 1 (X = $^+NH(CH_3)_2$), 81725-05-5; 1 (X = $^+N(CH_3)_3$) I^-, 81687-80-1; 1 (X = $^+N(CH_3)_3$) Cl^-, 81687-81-2; 1 (X = CH_3), 20417-60-1; 1 (X = C_2H_5), 81687-82-3; 1 (X = i-C_3H_7), 81687-83-4; 1 (X = t-C_4H_9), 81687-86-7; 1 (X = C_6H_5), 22947-58-6; 1 (X = p-$NO_2C_6H_4$), 60526-66-1; 1 (X = $Sn(CH_3)_3$), 78385-88-3; 1 (X = H), 20277-22-9; 1 (X = OH) K, 81725-06-6; 3 (X = NO_2), 63385-88-6; 3 (X = CN), 61541-38-6; 3 (X = CF_3), 81725-07-7; 3 (X = COOH), 68756-19-4; 3 (X = $CONH_2$), 81725-08-8; 3 (X = $CON(CH_3)_2$), 68756-35-4; 3 (X = $COOC_2H_5$), 68756-20-7; 3 (X = $COCH_3$), 64872-40-8; 3 (X = CHO), 68756-33-2; 3 (X = OH), 60526-68-3; 3 (X = OCH_3), 61541-36-4; 3 (X = $OCOCH_3$), 61565-42-2; 3 (X = F), 60526-63-8; 3 (X = Cl), 61541-33-1; 3 (X = Br), 61541-34-2; 3 (X = I), 61541-35-3; 3 (X = NH_2), 10207-00-8; 3 (X = $N(CH_3)_2$), 81725-09-9; 3 (X = $NHCOCH_3$), 10207-01-9; 3 (X = $^+NH_3$), 63385-89-7; 3 (X = $^+NH(CH_3)_2$), 81725-10-2; 3 (X = $^+N(CH_3)_3$) I^-, 81725-11-3; 3 (X = $^+N(CH_3)_3$) Cl^-, 81725-12-4; 3 (X = C_6H_5), 68756-32-1; 3 (X = p-$NO_2C_6H_4$), 68756-36-5; 3 (X = OH) K, 81725-13-5.

Potential Bile Acid Metabolites. 6.[1] Stereoisomeric 3,7-Dihydroxy-5β-cholanic Acids

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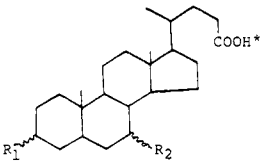
New synthetic routes to the four possible 3,7-dihydroxy acids are described. The principal reactions involved were inversions with DMF and Me_2SO–crown ether and reduction of 12-oxo tosylhydrazones. Inversion of 3α-tosylates by the Me_2SO–crown ether method succeeded but that of the corresponding mesylates did not. A table of ^1H NMR chemical shift reference data of monosubstituted methyl cholanates pertinent to bile acid characterization has been expanded.

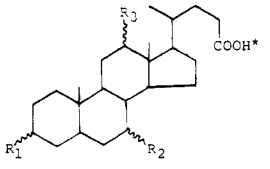
Of the four possible 3,7-dihydroxycholanic[3] acids, the 3α,7α [chenodeoxycholic (**1**)] and 3α,7β [ursodeoxycholic (**2**)] stereoisomers are commercial products, the 3β,7α isomer (**4**) is known but not generally available, and the 3β,7β isomer (**3**) has not been described[4] (see Chart I). As part of a program in our laboratory to make available potential bile acid metabolites for use as reference standards, and incidentally to reexamine existing methodology in bile acid synthesis, we have briefly reported new methods for preparing acids **1**[5] and **2**.[6] This paper covers synthesis of the two remaining stereoisomers of the 3,7-dihydroxy group, acids **3** and **4**, and presents additional details and observations encountered in the synthesis of acid **1** and alternative routes to acid **2**.

Conventional syntheses of the known 3,7 isomers involve reduction of the appropriate ketones, produced by selective oxidation, to the corresponding epimeric alcohols which are usually separated by chromatography. The syntheses herein reported do not proceed through intermediary ketones. The reactions used in the several syntheses are

Chart I



	R_1	R_2
1	α-OH	α-OH
2	α-OH	β-OH
3	β-OH	α-OH
4	β-OH	β-OH
5	β-OAc	α-OH
6	β-OAc	α-OMs
7	α-OMs	α-OMs
8	α-OMs	β-OH
9	α-OMs	H,H
10	α-OTs	α-OMs
11	α-OTs	α-OH
16	α-OAc	α-OAc
22	α-OCO_2Et	α-OH
23	α-OCO_2Et	α-OMs
24	α-OAc	α-OMs
27	α-OTs	β-OH
28	α-OAc	α-OH
29	α-OH	α-OAc
30	α-OCO_2Et	H,H



	R_1	R_2	R_3
12	α-OH	α-OH	=O
13	α-OAc	α-OAc	=NNHTs
14	α-OH	α-OH	=NNHTs
15	α-OH	α-OAc	=NNHTs
17	α-OH	α-OAc	=O
18	α-OAc	α-OAc	=O
19	α-OH	α-OH	α-OH
25	α-OH	β-OH	=O
26	α-OH	β-OH	=NNHTs

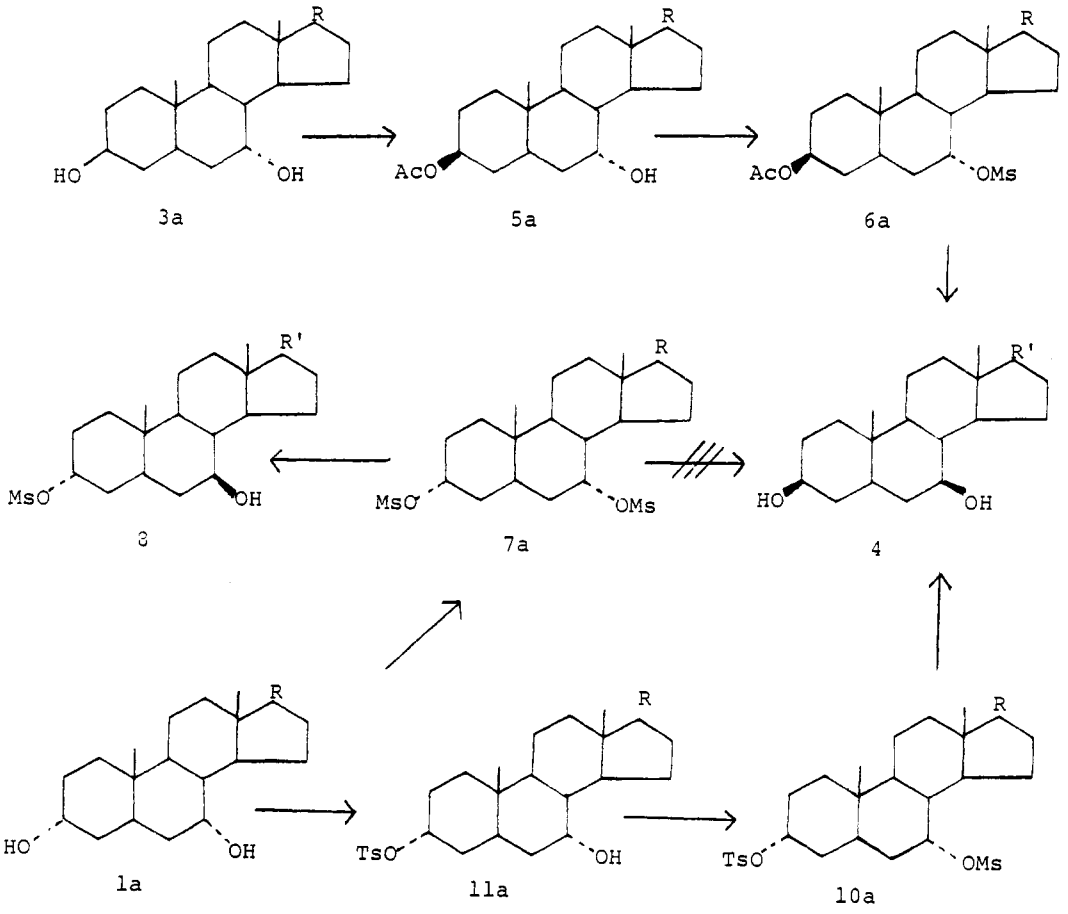
*The corresponding C-24 methyl esters are designated "a".

either direct inversions of an α-hydroxy derivative or conversion of a 12-oxo compound to its methylene analogue. Inversion of C-3 tosylates can be effected either by a previously described DMF reaction or a newly applied KO_2–crown ether reaction, while the C-7 hydroxy inversion

(1) Paper 5 of the series: F. C. Chang, *Synth. Commun.* 11, 875 (1981).
(2) On leave, Nihon University, Japan.
(3) All cholanic acid derivatives in this work are of the 5β series; the 5β designations are omitted in their names. The older name cholanic acid is used throughout in place of the newer IUPAC-suggested "cholanoic acid".
(4) The 3β,7β-acid **4** was mentioned in the patent literature [Japanese Kokai 77 78963; *Chem. Abstr.*, **87**, 201898 (1977)] as an undescribed minor product and was evidently prepared by reduction of methyl 7β-hydroxy-3-oxocholanate [B. Dayal, E. Bagan, C. S. Tint, S. Schefer and G. Salen, *Steroids*, 259 (1979)], but the product was characterized only by R_f (TLC) and t_R (GC) values.
(5) T. Iida and F. C. Chang, *J. Org. Chem.*, **46**, 2786 (1981). Both acids **1** and **2** are currently being used as gallstone-dissolving drugs. A. Steihl, P. Zygan, B. Komerell, H. J. Weis, and K. H. Holtermuller, *Gastroenterology*, **75**, 1016 (1978).
(6) T. Iida, H. R. Taneja, and F. C. Chang, *Lipids*, 16, 863.

0022-3263/82/1947-2966$01.25/0

Scheme I[a]



[a] R = $CH(Me)CH_2CH_2COOMe$ and R' = $CH(Me)CH_2CH_2COOH$.

succeeds only by the KO_2 reaction with a 7α-mesylate derivative. Syntheses of two of the isomers have also been carried out by $NaBH_4$–acetic acid reduction of 12-oxo tosylhydrazones.

3β,7β-Dihydroxycholanic Acid (4). Synthesis of this acid (its epimer in the 5α series is known[7]) was accomplished by two routes. The first is analogous to the preparation of **2**[6] from **1** by inversion at C-7; in this case the intermediate undergoing reaction was the 3β-acetoxy 7α-mesylate **6a**. The methyl ester **3a** was selectively acetylated at C-3 to give **5a** and converted to **6a** (Scheme I), which in turn was inverted by the KO_2–crown ether reaction to **4** (overall yield from acetate **5a** was 79%).

A possibly direct route to **4**, by the simultaneous inversion of methyl 3,7-di-*O*-mesylchenodeoxycholate (**7a**) at both the 3 and 7 positions by the KO_2 reaction, when attempted, failed. The product of the reaction turned out to be 3-*O*-mesylursodeoxycholic acid (**8**), crystalline and in 75% yield. Inversion at C-7 had taken place, accompanied by the expected hydrolysis of the methyl ester to the free acid, but the mesyloxy group had remained intact. The inertness of the 3-mesyloxy group was confirmed by the conversion of methyl *O*-mesyllithocholate **9a** to *O*-mesyllithocholic acid **9**.

However, methyl 3-*O*-tosyl-7-*O*-mesylchenodeoxycholate (**10a**), when subjected to KO_2–crown ether standard conditions, was surprisingly[8] found to undergo inversion at both the 3- and 7-positions, although much more slowly at C-3 than at C-7. As estimated by TLC monitoring, inversion at C-7 takes place about 10 times faster than at C-3.[9]

3β,7α-Dihydroxycholanic Acid (3). This acid had been prepared previously[10] by catalytic hydrogenation of the corresponding 3-keto compound and subsequent chromatographic separation of the resultant 3-hydroxy epimers. A simpler alternative route to **3** based on earlier studies[12] on the inversion of equatorial 3-hydroxy steroids is by the treatment of methyl 3-*O*-tosylchenodeoxycholate (**11a**) with *N*,*N*-dimethylformamide (DMF) at 80 °C.

A second procedure for obtaining **3** from **11a** emerged from the finding (above) that 3α-tosyloxy, unlike 3α-mesyloxy, does undergo inversion in the KO_2 reaction. Of the two reactions for preparing **3**, the DMF route is preferable because of its superior yield, easier workup, and lower reagent costs.

3α,7α-Dihydroxycholanic (Chenodeoxycholic) Acid (1). Despite the many problems associated with the procedure,[11] the only feasible preparation of acid **1** on a substantial scale appears to be by the Wolf–Kishner–

(7) S. A. Ziller, Jr., P. A. Houser, and W. H. Elliott, *Steroids*, **23**, 221 (1974).

(8) The preparation of 3-sulfonate derivatives of cholanic acids (not esters) has not been reported. 3-*O*-Tosylursodeoxycholic acid (**27**) for instance, which might have resulted from the tosylate mesylate **10a**, would be a useful new compound.

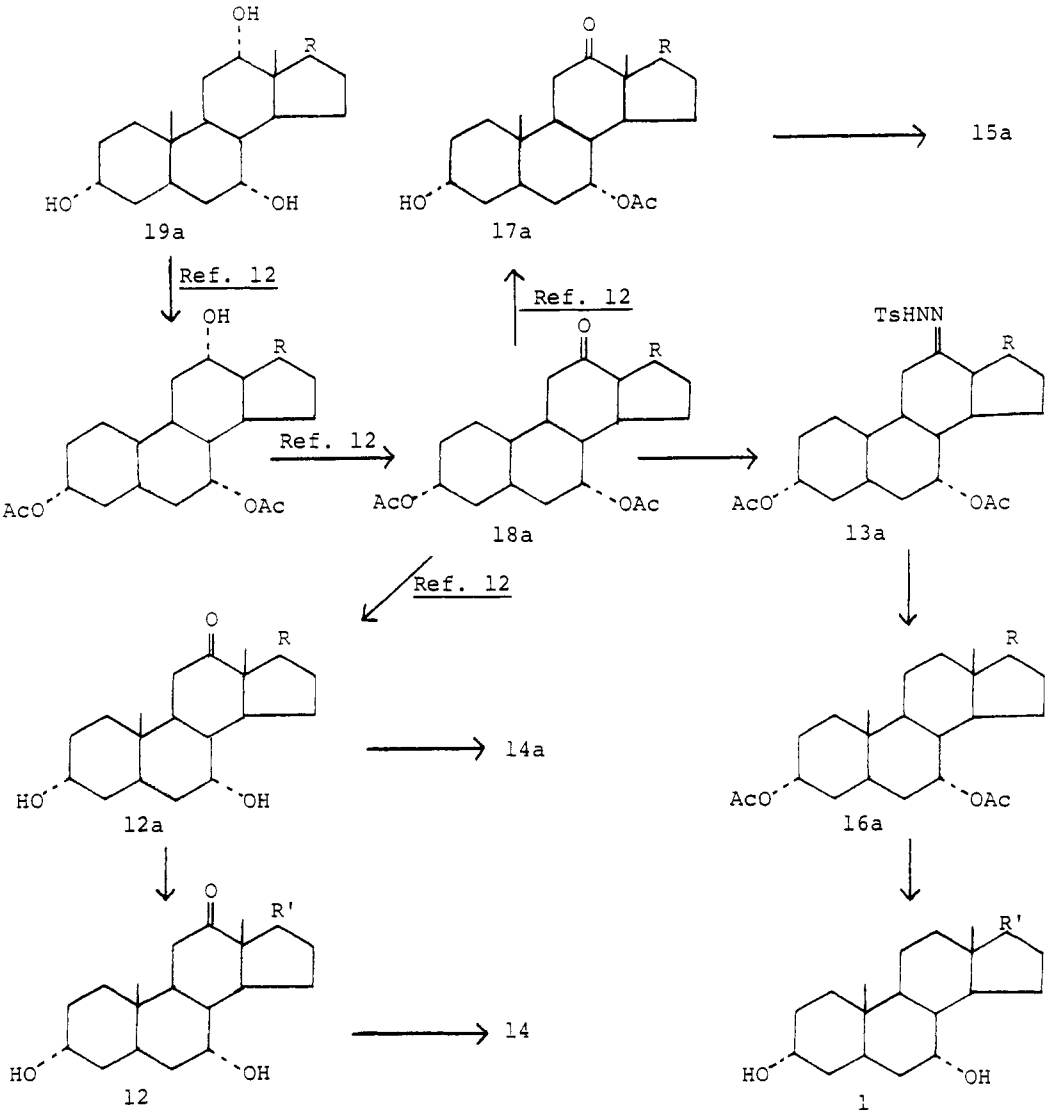
(9) In a comparison by TLC monitoring of the rates of the KO_2–crown ether reaction on the two compounds, the dimesylate **7a** and the tosylate mesylate **10a**, under the standard conditions after 22 h when **10a** had completely reacted, there was no indication of reaction of the 3α-mesyloxy group of **7a**; evidently if inversion takes place, it does so at an extremely low rate. The inertness of the 3-mesyloxy group is puzzling as tosylates and mesylates generally behave similarly; for instance, in the DMF inversion[12] 3α-mesylates also react.

(10) H. Danielsson, P. Eneroth, K. Hellström, and J. Sjövall, *J. Biol. Chem.*, **237**, 3657 (1962).

(11) Problems discussed: (a) E. Hauser, E. Baumgarten, and K. Meyer, *Helv. Chim. Acta*, **43**, 1595 (1966); (b) A. F. Hofmann, *Acta Chem. Scand.*, **17**, 173 (1963).

(12) F. C. Chang, *J. Org. Chem.*, **44**, 4567 (1979). This paper contains references to earlier work (footnotes 5 and 16) and a summary of other inversion methods evaluated (footnote 17).

Scheme II[a]



[a] R = $CH(Me)CH_2CH_2COOMe$ and R' = $CH(Me)CH_2CH_2COOH$.

Huang–Minlon method in which a derivative of 3α,7α-dihydroxy-12-oxocholanic acid (**12**), readily obtained from cholic acid,[12] is the starting material.[13] The strong basic and high-temperature conditions create a product which required tedious processing and purification before the desired acid **1** is obtained. A new method recently described in brief form[5] is much simpler and cleaner. Herein we report additional details pertinent to the new process.

Preliminary experiments exploring a method suggested by the publication of Hutchins and Natale[14] indicated that conversion of **12** to **1** via a 12-oxo tosylhydrazone was feasible, and that a satisfactory procedure could result by finding (a) the optimum conditions for reducing the tosylhydrazone, (b) the specific tosylhydrazone most suitable for the reduction, and (c) the best preparation of the selected tosylhydrazone.

It was evident from the exploratory work that reduction of the tosylhydrazone by $NaBH_4$ in acetic acid had to be conducted under the mildest feasible conditions, and even the slightly elevated temperatures suitable for other keto tosylhydrazones[15] lowered the quality of the final product.

Of the related tosylhydrazone derivatives evaluated in the reduction step, **14**, **14a**, **15a** and **13a**, methyl 3α,7α-diacetoxy-12-oxocholanate tosylhydrazone (**13a**) was clearly superior; methyl di-*O*-acetylchenodeoxycholate **16a**, obtained earlier from **13a** in crystalline form and good yield, was hydrolyzed to acid **1** nearly quantitatively.

Our previous experience of preparing tosylhydrazones of 12-oxocholane derivatives[15] by literature methods[16] by refluxing the ketone and *p*-toluenesulfonohydrazide in ethanol (or methanol) solution had been unsatisfactory; the product was contaminated with the corresponding azine. By addition of a catalytic amount of HCl to the solution the product was freed of azine. However, when the diacetate–ketone **18a** was treated in this manner, the reaction was incomplete even after 12 h, but, surprisingly, with a change of solvent to acetic acid the reaction proceeded smoothly and completely at room temperature to yield **13a**. The related tosylhydrazones **14**, **14a**, and **15a** also were prepared in this manner, but **13a** was the most easily isolated from the respective reaction products and afforded the best yield.

Thus **13a**, by virtue of its superiority in both the preparation and reduction steps, combined with the coincidence

(13) In ref 5 we inadvertently neglected to cite the work of C. H. Chen [*Synthesis*, 125 (1976); U.S. Patent 3 998 839; *Chem. Abstr.*, **86**, 124635 (1976)] which describes an alternate route to **1**.

(14) R. O. Hutchins and N. R. Natale, *J. Org. Chem.*, **43**, 2299 (1978).

(15) F. C. Chang, *J. Org. Chem.*, **20**, 2053 (1965).

(16) L. Cagliotti and M. Magi, *Tetrahedron Lett.*, 1261 (1962); R. O. Hutchins, C. A. Milewaki, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).

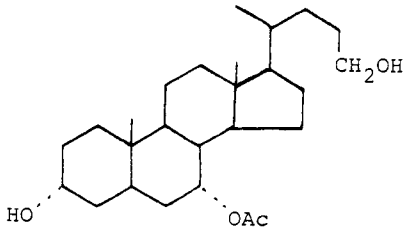
Table I. ^{1}H NMR Reference Data[a]

methyl cholanate deriv	CHOR[b] config[c]	CHOR[b] δ[d]	CHOR[b] $W_{1/2}$[e]	Me shifts[a] C-19	Me shifts[a] C-18	Me shifts[a] other
H,H (unsubstituted)				0.90	0.63	
3α-OH	ax	3.6[f]	16	0.93	0.65	
3β-OH	eq	4.07	8	0.92	0.67	
7α-OH	eq	3.92	9	0.90	0.66	
7β-OH	ax	3.58[f]	17	0.93	0.68	
12α-OH	eq	3.97	9	0.90	0.68	
12β-OH	ax	3.44[f]	16	0.94	0.72	
3α-OAc	ax	4.73	16	0.92	0.64	1.99 (OCOMe)
3α-OTs	ax	4.35	4	0.87	0.62	2.43 (ArMe), 7.30 and 7.75 (para-disubstituted phenyl, each 2 H, d, J = 8 Hz)
3α-OMs[24]	ax	4.65	16	0.92	0.64	2.98 (SO_2Me)
3α-OCO_2Et[25]	ax	4.56	14	0.93	0.64	4.28 (q, CH_2), 1.30 (t, CH_3, J = 7 Hz)
3β-OAc	eq	5.08	9	0.96	0.64	2.02 (OCOMe)
7α-OAc	eq	4.90	9	0.93	0.66	2.00 (OCOMe)
7α-OMs	eq	4.90	7	0.91	0.66	2.99 (SO_2Me)
7β-OAc	ax	4.79	17	0.93	0.66	1.94 (OCOMe)
3β-OCHO	eq	5.25	8	0.97	0.67	8.1 (OCHO)
3-Oxo				1.02	0.68	
7-Oxo				1.18	0.64	
12-Oxo				1.02	1.02	
12-OMs	eq	5.12	7	0.91	0.75	3.02 (SO_2Me)
12-Oxotosylhydrazone				0.94	0.82	2.41 (ArMe), 7.31 and 7.82 (para-disubstituted phenyl, each 2 H, d, J = 8 Hz)

[a] Data from Table I of ref 12 with corrected values [*J. Org. Chem.*, **46**, 2603 (1981)] are incorporated in this table; signals are derived from spectra of monosubstituted methyl cholanates pertinent to characterization of compounds in this work (solvent $CDCl_3$; Me_4Si as an internal standard). [b] Proton signal geminal to substituent at C-3, C-7, or C-12. [c] Conformation of H geminal to substituent: axial or equatorial. [d] Approximate center of multiplet. [e] Width of multiplet at half-height (in hertz). [f] Partly merged with OMe signal.

that the only practical route to the 3α,7α-dihydroxy-12-oxocholanate derivatives is via methyl 3α,7α-bis(acetoxy)-12-oxocholanate (**18a**), is clearly the intermediate of choice in the conversion of cholic acid (**19**) to chenodeoxycholic (**1**) by this method, as depicted in Scheme II.

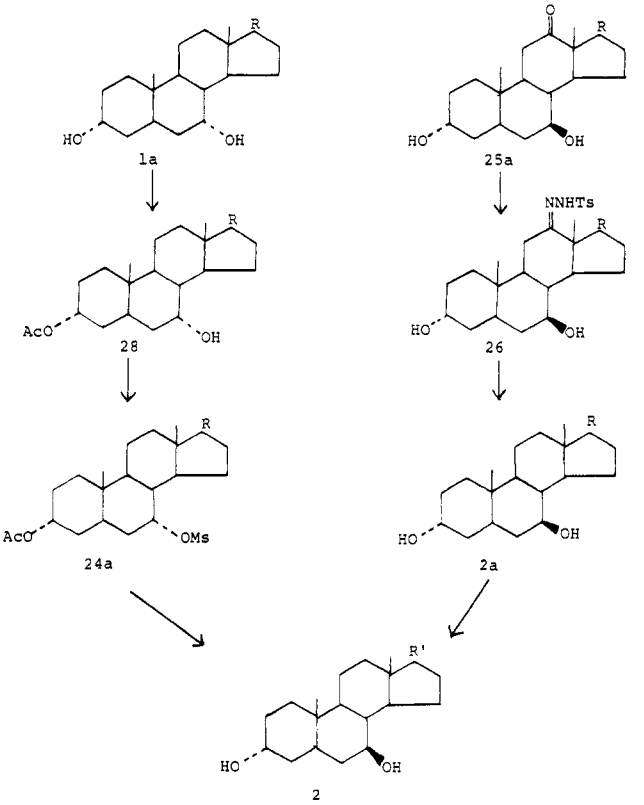
The method regarded by Cagliotti and Grasselli[17] to be a mild procedure for reducing carbonyl to methylene by refluxing the carbonyl tosylhydrazone in methanol (or dioxane) when applied to **13a** does produce a methylene group at C-12, but, as might be expected,[18] it also reduces the C-24 carbomethoxy group to CH_2OH, with simultaneous hydrolysis of the 3-acetoxy group. The product, 7-acetoxy-3α,24-cholandiol (**20**), is also obtained when the monoacetate tosylhydrazone **15a** is reduced under identical conditions.



20

3α,7β-Dihydroxycholanic (Ursodeoxycholic) Acid (2). A new route to **2** was described recently[6] which involves inversion at C-7 of methyl 3-*O*-cathyl-7-*O*-mesylchenodeoxycholate (**23a**). Herein we report two additional preparations of **2**. The first is merely an adaptation of the same procedure;[19] instead of the cathylate mesylate **23a**, the compound subjected to the inversion reaction is the acetate mesylate **24a** (Scheme III). In this instance the 3α,7α ester **1a**, selectively acetylated at C-3, was isolated

Scheme III[a]



[a] R = $CH(Me)CH_2CH_2COOMe$ and R' = $CH(Me)CH_2CH_2COOH$.

but without further processing was converted to **24a** which after crystallization underwent reaction in the KO_2–crown ether reagent to give **2** (yield based on **1a** 48%).

The second additional preparation of **2** is analogous to the preparation of **1** through the tosylhydrazone **13a**. Methyl 3α,7β-dihydroxy-12-oxocholanate tosylhydrazone (**26a**), accordingly, by $NaBH_4$–HOAc reduction yields

(17) L. Cagliotti and P. Grasselli, *Chem. Ind. (London)*, 153 (1964).
(18) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **18**, 3261 (1963); E. Schenker, *Angew. Chem.*, **73**, 81 (1961).
(19) However, in the process described in ref 6 the starting methyl chenodeoxycholate was carried through to **23a** without isolation of the cathylate **22a**.

Table II. KO_2-Crown Ether Inversion Reactions[a]

compd	product[b]	% yield	comments
23a	2	87[c]	
24a	2	48 (from 1a)	
11a	3	66	22-h reaction
6a	4	79 (from 5a)	
10a	4	62	22-h reaction
7a	8	75	no inversion at C-3
9a	9	76	no inversion at C-3

[a] KO_2-crown-6 ether in Me_2SO under N_2; all reaction periods were 2–3 h, except for **10a** and **11a** (22 h). [b] All products were 24-acids.

methyl ursodeoxycholate (**2a**). However, the key intermediate in this procedure, methyl 3α,7β-dihydroxy-12-oxocholanate (**25a**), currently is obtainable only through a multistep synthesis,[20] so that at present the method for preparation of **2** is less practical than one of the procedures starting from chenodeoxycholic acid (**1**).

Characterization of Compounds by NMR and HPLC. Table I is an extension of the corresponding table of ref 12.[30] All values were derived from monosubstituted methyl 5β-cholanate derivatives and thus are directly applicable to 5β-cholanate derivatives and thus are directly applicable to 5β bile acids, more so than the ones from previous compilations[26] derived from various classes of steroids. Characterization of the compounds reported in this work was facilitated by applying these data, supported by specific mechanistic knowledge regarding the reactions used.

NMR and HPLC were extremely useful for the assessment of the purity of a product, especially a noncrystalline compound. Moreover, these techniques enable one to rapidly evaluate and develop a new reaction, complementing conventional monitoring by TLC.

The four 3,7-dihydroxy stereoisomeric methyl esters are well resolved by HPLC,[27] emerging from a reverse-phase column in the following order: 3α,7β; 3β,7β; 3β,7α; 3α,7α. The solvent system used was methanol–water (90:10) at a flow rate of 0.5 mL/min.

KO_2–Crown Ether Inversion Reactions. Product and yield data for these reactions are given in Table II.

Experimental Section[28]

General Procedures for Preparation of Derivatives. Where a general procedure is used, details of the preparation, including processing of the product, are described fully only in the first such preparation: i.e., mesylation of **7a**-hydroxy compounds (**6a**), inversion with KO_2–crown ether (**4**), preparation of 12-oxo tosylhydrazones (**13a**), and reduction of tosylhydrazones (**16a**). Only in instances of departure from the general procedure are details included in the other experimental descriptions.

Methyl 3β-Acetoxy-7α-hydroxycholanate (5a). To the 3β,7α-dihydroxy ester **3a** (656 mg) dissolved in 5 mL of benzene and 2 mL of pyridine was added 1 mL of acetic anhydride. After the mixture was allowed to stand overnight at room temperature and processed as usual, the residue was chromatographed on a column of Al_2O_3 (neutral, grade II). The benzene-eluted fractions after evaporation (424 mg) crystallized from aqueous acetone as colorless thin plates: mp 89–92 °C; IR ($CHCl_3$) 1718 (C=O), 1018 (acetate), 988 (COH) cm^{-1}; NMR δ 0.69 (3 H, s, C-18 Me), 0.98 (3 H, s, C-19 Me), 2.03 (3 H, s, OCOMe), 3.65 (3 H, s, COOMe), 3.88 (1 H, m, C-7 CHOH), 5.02 (1 H, m, C-3 CHOAc).

Continued elution with benzene–ethyl acetate (1:1) gave 194 mg of starting ester **3a**.

Anal. Calcd for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89. Found: C, 72.37; H, 10.03.

Methyl 3β-Acetoxy-7α-(mesyloxy)cholanate (6a). To methyl 3β-acetoxy-7α-hydroxycholanate (**5a**; 1.4 g, 3.1 mmol) magnetically stirred in 14 mL of dry pyridine was slowly added dropwise 1.5 mL (6.2 equiv) of methanesulfonyl chloride. Stirring was continued for 1 h and the mixture then allowed to stand overnight at room temperature. The dark solution was dripped into a mixture of ice chips in water, stirred, and extracted with CH_2Cl_2 (2×). The combined CH_2Cl_2 extract was washed successively with ice, cold dilute HCl, 5% $NaHCO_3$ solution, and H_2O, decolorized with Norite, and evaporated. The residual oil, **6a**, crystallized from benzene–hexane in the form of fine needles: 1.08 g (66%); mp 101.0–101.5 °C. The mother liquor yielded a second crop of crystals: 300 mg (19%); mp 98.8–99.5 °C; IR ($CHCl_3$) 1724 (C=O), 1294, 1172 (SO_2), 1024 (acetate), 893 (mesylate) cm^{-1}; NMR δ 0.69 (3 H, s, C-18 Me), 0.99 (3 H, s, C-19 Me), 2.03 (3 H, s, OCOMe), 3.00 (3 H, s, SO_2Me), 3.66 (3 H, s, COOMe), 4.93 (1 H, m, C-7, CHOMs), 5.06 (1 H, m, C-3 CHOAc).

Anal. Calcd for $C_{28}H_{46}O_7S$: C, 63.85; H, 8.80. Found: C, 64.13; H, 9.05.

Methyl 3-*O*-tosyl-7-*O*-mesylchenodeoxycholate (10a) was prepared by the general mesylation procedure from methyl 3-*O*-tosylchenodeoxycholate[21] (**11a**), mp 134.5–136.0 °C (from benzene–hexane). The product crystallized from benzene–hexane as round tufts of colorless leaflets: mp 80.0–81 °C (yield 65%); IR ($CHCl_3$) 1724 (C=O), 1342, 1328, 1183, 1170 (SO_2), 893 (mesylate) cm^{-1}; NMR δ 0.64 (3 H, s, C-18 Me), 0.90 (3 H, s, C-19 Me), 2.43 (3 H, s, ArMe), 2.96 (3 H, s, SO_2Me), 3.64 (3 H, s, COOMe), 4.33 (1 H, br m, C-3 CHOTs), 4.89 (1 H, m, C-7 CHOMs), 7.31 and 7.78 (each 2 H, d, J = 8 Hz, para-disubstituted phenyl).

Anal. Calcd for $C_{33}H_{50}O_8S_2 \cdot {}^1/_6C_6H_{14}$: C, 62.55; H, 8.03. Found: C, 62.36; H, 8.30.

Methyl 3,7-di-*O*-mesylchenodeoxycholate (7a) was prepared from **1a** by the general mesylation procedure with an additional equivalent of methanesulfonyl chloride. The residual extract, although found to be homogeneous by TLC and NMR, resisted crystallization efforts: IR ($CHCl_3$) 1724 (C=O); 1342, 1328, 1170 (SO_2); 971, 922, 893, 870 (mesylate) cm^{-1}; NMR δ 0.64 (3 H, s,

(20) Preparation of methyl 3α,7β-dihydroxy-12-oxocholanate (**25a**) is described in the accompanying paper in this issue (part 7 of this series).

(21) J. T. Baker and R. T. Blickenstaff, *J. Org. Chem.*, **40**, 1579 (1975).

(22) The Me_2SO–1,2-dimethoxyethane solvent mixture was used to increase solubility of the mesylate; in most other cases Me_2SO alone was a satisfactory solvent.

(23) At this stage benzene extraction to remove the nonpolar products (Me_2SO, crown ether, dimethyl sulfone) is essential. These contaminants are difficult to remove even by column chromatography.

(24) Methyl *O*-mesyllithocholate (**9a**), prepared with methanesulfonyl chloride and pyridine, was crystallized from benzene–hexane: mp 129.5–132 °C; NMR δ 0.64 (3 H, s, C-18 Me), 0.92 (3 H, s, C-19 Me), 2.98 (3 H, s, SO_2Me), 3.65 (3 H, s, COOMe), 4.65 (1 H, br m, C-3 CHOMs).

(25) Methyl *O*-cathyllithocholate (**30a**), prepared from ethyl chlorocarbonate and pyridine in dioxane, was crystallized from MeOH: mp 135.0–137.0 °C; NMR δ 0.64 (3 H, s, C-18 Me), 0.93 (3 H, s, C-19 Me), 1.80 (3 H, t, J = 8 Hz, OCH_2CH_3), 3.65 (3 H, s, COOMe), 4.18 (2 H, q, J = 8 Hz OCH_2CH_3), 4.56 (1 H, br m, C-3 $CHOCO_2Et$).

(26) R. H. Zurcher, *Helv. Chim. Acta*, **46**, 2054 (1963); N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, 1964, pp 47, 77.

(27) The HPLC instrument used was a Waters Associates assembly with a septumless injector and refractive index detector. Of the C-18 reverse-phase columns tried, Bondapak (Waters), Radial Compression (Waters), and Excalibar (Applied Science), the last two gave excellent resolutions, but the Radial Compression column allowed the chromatography to be performed at a lower pressure (a desirable feature).

(28) Melting points were determined on an electrical micro hot stage and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer infracord spectrophotometer. NMR spectra were determined with a Perkin-Elmer R-32 instrument, with deuteriochloroform containing Me_4Si as the solvent except where otherwise indicated. The TLC development solvent used for the 3,7-hydroxy derivatives was $CHCl_3$–EtOAc–HOAc (45:45:10). Solvents were evaporated on a Rotavap at 50 °C under reduced pressure. All bile acid derivatives were dried by azeotropic distillation [benzene, benzene–CH_2Cl_2, CH_2Cl_2, or CH_2Cl_2–MeOH (acids)] before use in reactions.

C-18 Me), 0.93 (3 H, s, C-19 Me), 2.98 and 3.00 (each 3 H, s, C-3 and C-7 SO_2Me), 3.62 (3 H, s, COOMe), 4.49 (1 H, br m, C-3 CHOMs), 4.89 (1 H, m, C-7 CHOMs).

Anal. Calcd for $C_{27}H_{46}O_8S_2 \cdot {}^1/_6C_6H_{14}$: C, 58.31; H, 8.39. Found: C, 58.57; H, 8.53.

Methyl 3-*O*-Acetyl-7-*O*-mesylchenodeoxycholate (24a). Methyl 3-*O*-acetylchenodeoxycholate (**28a**)[21] was first prepared by monoacetylation of methyl chenodeoxycholate (400 mg; Ac_2O, C_6H_6, pyridine). After isolation of **28a** by the usual method, without crystallization, the residual oil was mesylated by the standard procedure to afford, after recrystallization from isopropyl ether–MeOH, 190 mg (37% from **1a**) of **24a**: mp 95.0–95.5 °C; IR ($CHCl_3$) 1724 (C=O); 1330, 1170 (SO_2), 1024 (acetate), 894 (mesylate) cm^{-1}; NMR δ 0.71 (3 H, s, C-18 Me), 1.00 (3 H, s, C-19 Me), 2.05 (3 H, s, OCOMe), 3.04 (3 H, s, SO_2Me), 3.64 (3 H, s, COOMe), 4.61 (1 H, br m, C-3 CHOAc), 4.91 (1 H, m, C-7 CHOMs).

Anal. Calcd for $C_{28}H_{46}O_7S \cdot CH_3OH$: C, 62.34; H, 9.02. Found: C, 62.61; H, 8.87.

3β,7β-Dihydroxycholanic Acid (4). (a) The inverting solution was first prepared by magnetically stirring for 10 min under nitrogen 120 mg of powdered KO_2 in 10 mL of Me_2SO. 18-Crown-6 ether (75 mg) was added and stirring continued for an additional 10 min. Into this yellow turbid solution was pipetted 251 mg (0.4 mmol) of the acetate mesylate **6a** dissolved in 1 mL of Me_2SO–1,2-dimethoxyethane.[22] Stirring was continued under N_2 for 2 h; the reaction was monitored by TLC. The flask was immersed in an ice bath, and as the solution was stirred, 12 mL of saturated NaCl was added. The resulting solution, after reaching room temperature, was extracted with benzene (2 × 30 mL).[23] The cooled basic aqueous layer was acidified by cold 3 N HCl to turbidity and extracted with EtOAc (2×). The EtOAc extract was washed with water, dried (Drierite), and evaporated to a residue (183 mg) which crystallized from EtOAc–hexane as round tufts of needles: mp 166.0–168.5 °C; 147 mg (79%); IR (KBr) 1709 (C=O), 1031 (3β-COH); 1016 (7β-COH) cm^{-1}; NMR δ 0.71 (3 H, s, C-18 Me), 1.00 (3 H, s, C-19 Me), 3.65 (1 H, br m, C-7 CHOH), 4.07 (1 H, m, C-3 CHOH).

Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.53; H, 10.45.

(b) Methyl 3-*O*-tosyl-7-*O*-mesylchenodeoxycholate (**10a**, 830 mg) by the same inversion procedure yielded the 3β,7β-acid, but the complete reaction required 22 h (as monitored by TLC). After two recrystallations from ethyl acetate, 334 mg (62%) of **4** was obtained as colorless fine needles (mp 166.0–167.5 °C), shown to be identical with the product of part a by NMR, TLC, and melting point comparisons.

Methyl 3β,7β-dihydroxycholanate (4a) prepared from **4** by the usual MeOH–HCl method crystallized from aqueous acetone as colorless, fine, rectangular plates: mp 124.0–125.0 °C; IR ($CHCl_3$) 1724 (C=O), 1029 (3β-COH), 1015 (7β-COH) cm^{-1}; NMR δ 0.71 (3 H, s, C-18 Me), 1.00 (3 H, s, C-19 Me), 3.55 (1 H, br m, C-7 CHOH), 3.65 (3 H, s, COOMe), 4.04 (1 H, m, CHOH).

Anal. Calcd for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 73.67; H, 10.46.

3α-(Mesyloxy)-7β-hydroxycholanic acid (8) was obtained from the dimesylate **7a** (370 mg) by the standard inversion procedure. As monitored by TLC, no 3β,7β-acid had formed after 22 h of reaction time. Crystallized from EtOAc–hexane as thin plates, **8** had the following: mp 124–126 °C; 232 mg (75%); IR ($CHCl_3$) 1704 (C=O), 1351, 1325, 1168 (SO_2), 1015 (C-7 COH), 926, 909, 871 (mesylate) cm^{-1}; NMR δ 0.70 (3 H, s, C-18 Me), 0.97 (3 H, s, C-19 Me), 2.98 (3 H, s, SO_2Me), 3.56 (1 H, br m, C-7 CHOH), 4.58 (1 H, br m, C-3 CHOMs).

Anal. Calcd for $C_{25}H_{42}O_6S$: C, 63.80; H, 9.00. Found: C, 64.07; H, 9.16.

***O*-Mesyllithocholic Acid (9).** The standard inversion procedure with 450 mg of methyl *O*-mesyllithocholate (**9a**),[24] in 8 h, simply resulted in hydrolysis of the methyl ester, and **9** crystallized from EtOAc–hexane as fine needles: mp 155.5–157.0 °C 333 mg (76%); IR (KBr) 1733 (C=O), 1351, 1330, 1170, 997, 971, 955, 923, 913, 897 (C-3 mesylate) cm^{-1}; NMR δ 0.67 (3 H, s, C-18 Me), 0.96 (3 H, s, C-19 Me), 3.00 (3 H, s, SO_2Me), 4.64 (1 H, br m, C-3 CHOMs).

Anal. Calcd for $C_{25}H_{42}O_5S \cdot {}^1/_6C_6H_{14}$: C, 66.64; H, 9.46. Found: C, 66.72; H, 9.46.

Methyl 3β,7α-Dihydroxycholanate (3a). Methyl 3-*O*-tosylchenodeoxycholate (**11a**,[21] 2.25 g) was inverted to the 3β-formate by the DMF procedure as previously described.[12] The crude formate dissolved in benzene was placed on a column of neutral alumina (grade I, ratio 50:1) and left for 18 h. Elution with benzene yielded 0.67 g of a mixture of less polar compounds (consisting mainly of the 7α-hydroxy-3-cholenate).[12] Elution was continued with CH_2Cl_2–MeOH (98:2), giving an oil (1.04 g) which crystallized from aqueous methanol as fine needles: mp 156.5–158.5 °C [lit.[10] mp 155 °C (from acetone–H_2O)]; 0.91 g (56%); IR ($CHCl_3$) 1721 (C=O); 1072, 1031, 1002, 980 (COH) cm^{-1}; NMR δ 0.68 (3 H, s, C-18 Me), 0.96 (3 H, s, C-19 Me), 3.66 (3 H, s, COOMe), 3.87 (1 H, m, C-7 CHOH), 4.06 (1 H, m, C-3, CHOH).

Anal. Calcd for $C_{25}H_{42}O_9$: C, 73.85; H, 10.41. Found: C, 74.01; H, 10.57.

3β,7α-Dihydroxycholanic Acid (3). (a) Methyl ester **3a** by the usual methanolic KOH method, followed by acidification and recrystallization from EtOAc–hexane, gave **3** as dense crystals: mp 204.0–206.0 °C (from EtOAc), 193.0–195.0 °C (from acetone–petroleum ether) (lit.[10] mp 193 °C); IR (KBr) 1715 (C=O), 1071, 1034, 1003, 982 (COH) cm^{-1}; NMR δ 0.67 (3 H, s, C-18 Me), 0.94 (3 H, s, C-19 Me), 3.87 (1 H, m, C-7, CHOH), 4.07 (1 H, m, C-3 CHOH).

Anal. Calcd for $C_{24}H_{40}O_4 \cdot {}^1/_6C_4H_8O_2$: C, 72.72; H, 10.23. Found: C, 72.93; H, 10.27.

(b) Methyl 3-*O*-tosylchenodeoxycholate (**11a**,[21] 940 mg), subjected to the KO_2–crown ether inversion procedure, required 22 h for complete reaction (monitored by TLC). The acid **3** recrystallized from EtOAc in the form of small prisms: [347 mg (52%); mp 193.0–195.0 °C] identical with **3** from part a by NMR and TLC comparisons.

Methyl 3α,7α-Diacetoxy-12-oxocholanate Tosylhydrazone (13a). To methyl 3α,7α-diacetoxy-12-oxocholanate (**18a**; 10.1 g, 0.02 mol), stirred in 200 mL of acetic acid, was added gradually 7.5 g (0.04 mol) of *p*-toluenesulfonohydrazide. After being allowed to stand 12 h at room temperature, the mixture was diluted with water and extracted with CH_2Cl_2 (2×). The combined CH_2Cl_2 extract was washed with 5% $NaHCO_3$ solution and then with H_2O to neutrality, dried with Drierite, and evaporated to an oil which, when treated with a small volume of methanol, crystallized. Recrystallization in methanol yielded 9.7 g (72%) of **13a** as fine needles, mp 146.0–147.0 °C. (Complete characterization reported in ref 5.)

Methyl 3α,7α-dihydroxy-12-oxocholanate tosylhydrazone (14a) was prepared by the general method from ester **12a** and crystallized from aqueous methanol as colorless needles: 52%; mp 204–206 °C; IR ($CHCl_3$) 1724 (C=O), 3195, 1626, 1592, 1330, 1163, 813 (tosylhydrazone)[15] cm^{-1}; NMR δ 0.78 (3 H, s, C-18 Me), 0.97 (3 H, s, C-19 Me), 2.41 (3 H, s, ArMe), 3.33 (1 H, br m, C-3 CHOH), 3.64 (3 H, s, COOMe), 3.84 (1 H, m, C-7 CHOH), 7.29 and 7.88 (each 2 H, d, J = 8 Hz, para-disubstituted phenyl).

Anal. Calcd for $C_{32}H_{48}N_2O_6S \cdot 0.50CH_3OH$: C, 64.54; H, 8.33. Found: C, 64.28; H, 8.13.

3α,7α-Dihydroxy-12-oxocholanic acid tosylhydrazone (14) was prepared from acid **12** by the general procedure. In this instance the reaction product, when diluted with water, precipitated. The precipitate, when recrystallized from aqueous methanol, appeared as colorless needles: 70%; mp 224.0–228.0 °C; IR (KBr) 1730 (C=O), 3205, 1634, 1600, 1333, 1163 (s), 814 (tosylhydrazone) cm^{-1}; NMR ($CDCl_3$ + 10% Me_2SO-d_6) δ 0.78 (3 H, s, C-18 Me), 0.93 (3 H, s, C-19 Me), 2.62 (3 H, s, ArMe), 3.33 (1 H, br m, C-3 CHOH), 4.21 (1 H, m, C-7 CHOH), 7.29 and 7.78 (each 2 H, d, J = 8 Hz, para-disubstituted phenyl).

Anal. Calcd for $C_{31}H_{46}N_2O_6S \cdot 0.50CH_3OH$: C, 64.40; H, 8.19. Found: C, 64.06; H, 8.12.

Methyl 3α-hydroxy-7α-acetoxy-12-oxocholanate tosylhydrazone (15a), prepared from **17a** by the general method, when diluted with water was a solid precipitate. The precipitate from 332 mg of **17a** was transferred to a separatory funnel with methylene chloride and $NaHCO_3$ solution. The CH_2Cl_2 solution was filtered through phase-separating paper and evaporated to a glassy solid, 384 mg. The solid resisted attempts at crystallization, although by HPLC it appeared to be homogeneous, and its NMR spectrum was in accord with that of the expected tosylhydrazone: NMR δ 0.81 (3 H, s, C-18 Me), 0.98 (3 H, s, C-19 Me), 2.02 (3 H, s, OCOMe) 2.41 (3 H, s, ArMe), 3.40 (1 H, br m,

C-3 CHOH), 3.90 (1 H, m, C-7 CHOAc), 7.32 and 7.88 (each 2 H, J = 8 Hz, para-disubstituted phenyl).

Methyl 3α,7β-dihydroxy-12-oxocholanate tosylhydrazone (26a) was prepared from 1.6 g of 3α,7β-dihydroxy-12-oxocholanate (**25a**)[20] by the general procedure. The residue crystallized from methanol as colorless thin plates: 1.44 g (64%); mp 244.0–247.0 °C; IR (KBr) 1718 (C=O), 3106, 1618, 1587, 1321, 1166 (s), 816 (tosylhydrazone) cm^{-1}; NMR ($CDCl_3$ + 10% Me_2SO-d_6) δ 0.79 (3 H, s, C-18 Me), 0.99 (3 H, s, C-19 Me), 2.41 (3 H, s, ArMe), 3.50 (2 H, br m, C-3 and C-7 CHOH), 3.64 (3 H, s, COOMe), 7.26 and 7.78 (each 2 H, d, J = 8 Hz, para-disubstituted phenyl).

Anal. Calcd for $C_{32}H_{48}N_2O_6S \cdot {}^1/_3CH_3OH$: C, 64.81; H, 8.30. Found: C, 64.81; H, 8.21.

Methyl Di-*O*-acetylchenodeoxycholate (16a).[5] To a magnetically stirred solution of acetic acid (80 mL) containing 4.04 g (0.006 mol) of **13a** was added 2.27 g (0.06 mol) of $NaBH_4$ (pellets) at a rate which did not allow the reaction temperature to exceed 60 °C (ca. 1 h). Stirring was continued at room temperature for 3 h, and then with the flask immersed in an ice bath, ice chips were gradually stirred in. The precipitated and filtered solid, after being washed with water, crystallized from aqueous methanol as fine needles: 1.58 g (53%); mp 133.0–133.5 °C (further characterization in ref 5).

Methyl Chenodeoxycholate (1a). (a) Reduction of 3α,7α-dihydroxy-12-oxocholanic acid tosylhydrazone (**14**) by the general procedure afforded a precipitate which did not crystallize, but according to TLC, **1** was predominant. The crude residue was esterified by MeOH–HCl treatment and chromatographed on a Florisil column. A fraction (72%) according to NMR, TLC and HPLC was homogeneous **1a**.

(b) Reduction of methyl 3α,7α-dihydroxy-12-oxocholanate tosylhydrazone (**14a**) by the general method when diluted with ice–H_2O precipitated as an oil. The aqueous residual mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extract, neutralized with $NaHCO_3$ solution, dried (Drierite), and chromatographed on an alumina (activity II) column, gave **1a** (57%), as confirmed by TLC, NMR, and hydrolysis to acid **1**.

Methyl Ursodeoxycholate (2a). Methyl 3α,7β-dihydroxy-12-oxocholanate tosylhydrazone (**26a**, 510 mg) reduced by the general method, yielded an oily residue which did not crystallize. Chromatographed on a Florisil column, the fractions eluted (33 mg) with CH_2Cl_2/EtOAc (1:1) were olefinic (tetranitromethane test). Further elution with EtOAc yielded **2a** which crystallized from aqueous methanol [182 mg (52%); mp 159–161 °C] and was identical with authentic methyl urosodeoxycholate according to mixture melting point, TLC, NMR, and HPLC comparisons.

7α-Acetoxy-3α,24-cholanediol (21). (a) Reduction of **13a** (1.0 g), according to the Cagliotti and Grasseli conditions,[17] by $NaBH_4$ in dioxane under reflux for 6 h yielded, after processing and crystallization from aqueous acetone, 412 mg (66%) of **21** as needles: mp 86.0–88.5 °C; IR ($CHCl_3$) 1721 (C=O), 1070, 969 (COH)8 1015 (OAc) cm^{-1}; NMR δ 0.67 (3 H, s, C-18 Me, 0.92 (3 H, s, C-19 Me), 2.03 (3 H, s, OCOMe), 3.45 (1 H, br m, C-3 CHOH), 3.56 (2 H, t, CH_2OH), 4.88 (1 H, m, C-7 CHOAc).

Anal. Calcd for $C_{26}H_{44}O_4 \cdot 0.30C_3H_6O$: C, 70.67; H, 10.51. Found: C, 70.56; H, 10.45.

(b) The tosylhydrazone **15a**, after reduction by $NaBH_4$–dioxane[29] as in part a, was chromatographed on activity II alumina. The CH_2Cl_2–MeOH (99:1) eluted material crystallized from aqueous MeOH as fine needles identical with the product of part a by mixture melting point, NMR, and HPLC comparisons.

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Registry No. **1a**, 3057-04-3; **2a**, 10538-55-3; **3**, 566-24-5; **3a**, 28050-38-6; **4**, 78919-26-3; **4a**, 73465-45-9; **5a**, 81857-19-4; **6a**, 81857-20-7; **7a**, 81938-69-4; **8**, 81875-58-3; **9**, 81857-21-8; **9a**, 81938-70-7; **10a**, 81875-59-4; **11a**, 28192-93-0; **12**, 2458-08-4; **12a**, 10538-64-4; **13a**, 76927-60-1; **14**, 79580-95-3; **14a**, 81875-60-7; **15a**, 81875-61-8; **16a**, 2616-71-9; **17a**, 71837-87-1; **18a**, 28535-81-1; **20**, 81857-22-9; **23a**, 81089-18-1; **24a**, 81857-23-0; **25a**, 81655-85-8; **26a**, 81857-24-1; **28a**, 19684-68-5; **30a**, 81857-25-2.

(29) Reduction of **15a** (amorphous) by the general procedure ($NaBH_4$–HOAc) afforded a complex mixture which contained methyl 7-*O*-acetylchenodeoxycholate (**29a**) as the major product, according to HPLC and NMR comparisons with authentic **29a**. However, the best fractions of **29a** obtained by column chromatography still contained impurities which inhibited crystallization. This route to chenodeoxycholic acid (**1**) was deemed inferior to the published method[5] and was not further pursued.

(30) Corrected values: F. C. Chang, *J. Org. Chem.*, **46**, 2603 (1981).

Potential Bile Acid Metabolites. 7.[1] 3,7,12-Trihydroxy-5β-cholanic Acids and Related Compounds

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With this work, the complete set of the eight possible stereoisomeric (5β)-3,7,12-trihydroxy acids are now known and characterized. The key intermediates methyl 3α,7β-dihydroxy-12-oxo- and 3β,7β-dihydroxy-12-oxocholanate have been synthesized, and their reductions by *tert*-butylamine–borane complex and by $NaBH_4$ are described.

The 3,7,12-trihydroxy stereoisomers of cholic (3α,7α,12α-trihydroxycholanic[3]) acid (**1**, Chart I) are of sustained interest in metabolic studies of the bile acids.[4] As part of a program to make available new and known, but generally unavailable, potential bile acid metabolites for such studies, three of the seven possible stereoisomers [3α,7α,12β (**2**), 3β,7α,12α (**3**), and 3β,7α,12β (**4**)] were synthesized and previously reported.[5] The present paper describes the syntheses of the four remaining members of this group and several related compounds and, in addition, presents improved preparations of **2** and **4**.

The 3α,7β,12α acid **5** was prepared by Samuelsson some years ago[6] by adaptation of a route used to obtain urso-

(1) Part 6 of this series: T. Iida and F. C. Chang, *J. Org. Chem.*, accompanying paper in this issue.

(2) On leave, Nihon University, Japan.

(3) All cholanic acid derivatives in this work are of the 5β series; the 5β designations are omitted in their names. The older name cholanic acid is used throughout in place of the newer IUPAC-suggested "cholanoic acid".

(4) There is epidemiological evidence that bile acid metabolites are implicated in colon carcinogenesis, and gastroenterological research has been involved for many years in exploring the role of bile acids in normal and abnormal metabolism.

(5) F. C. Chang, *J. Org. Chem.*, **44**, 4567 (1979).

(6) B. Samuelsson, *Acta Chem. Scand.*, **14**, 7 (1960). The number of requests received from investigators for samples of **5** attests to its rarity and need.

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