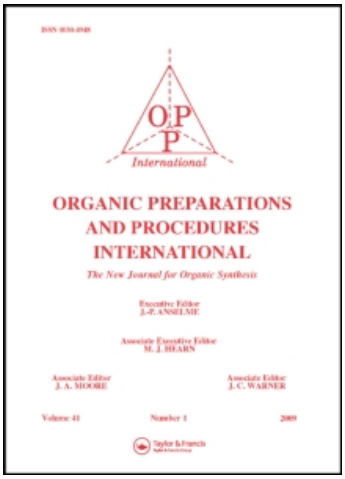

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF BIOLOGICAL MARKERS IN FOSSIL FUELS 5. A SYNTHESIS OF 5α-CHOLAN-24-OIC ACID

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To cite this Article Demir, Ayhan S. , Sabol, Mark R. , Jeganathan, Alwarsamy , Dolence, Eric Kurt , Watt, David S. and Moldowan, J. Michael(1987) 'SYNTHESIS OF BIOLOGICAL MARKERS IN FOSSIL FUELS 5. A SYNTHESIS OF 5α-CHOLAN-24-OIC ACID', Organic Preparations and Procedures International, 19: 2, 197 — 208

To link to this Article: DOI: 10.1080/00304948709356187

URL: http://dx.doi.org/10.1080/00304948709356187

ORGANIC PREPARATIONS AND PROCEDURES INT. 19(2-3), 197-208 (1987)

SYNTHESIS OF BIOLOGICAL MARKERS IN FOSSIL FUELS 5.[†]

A SYNTHESIS OF 5α-CHOLAN-24-OIC ACID

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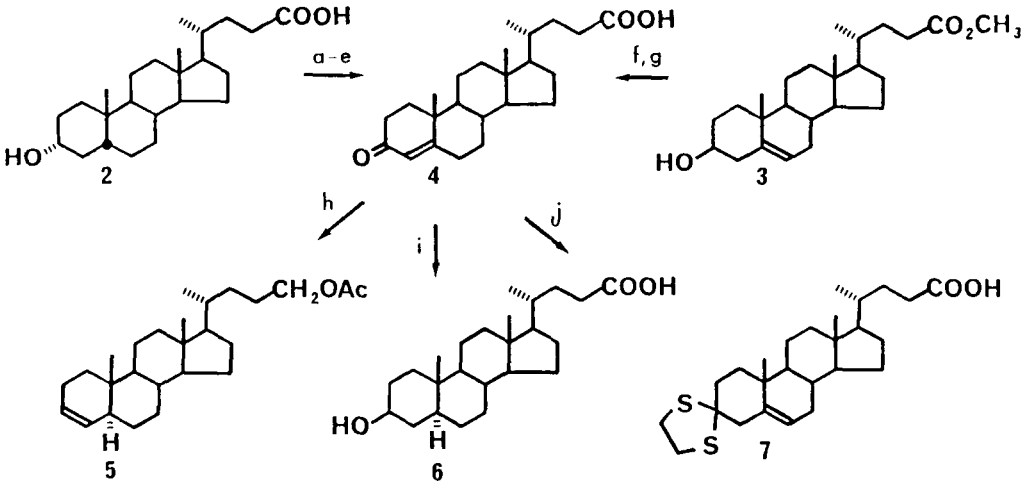
The side-chain degradation of C_{27}, C_{28}, and C_{29} steranes during the maturation and biodegradation of crude oils produces various hydrocarbon "biomarkers" of potential value in petroleum exploration.[1] In synthesizing various members of this group, we required an efficient synthesis of 5α-cholan-24-oic acid[2] (1) (or allocholanic acid). The bile acids constituted an obvious departure point for a synthesis of 1 in which the synthetic problems reduced to the epimerization of the natural 5β-configuration and the deoxygenation of an appropriate bile acid. Because 5α-cholan-24-oic acid is no longer available commercially, we report a synthesis of 1 on a gram scale.

We developed an efficient route to 3-oxo-4-cholen-24-oic acid (4) as shown in Scheme 1 from the inexpensive precursor, lithocholic acid (2), or from the more expensive material,

methyl 3β-hydroxy-5-cholen-24-oate (3), but we were unable to reduce selectively and efficiently the enone functionality in 4 to give the 5α-stereochemistry. Reduction[3] of 4 with

Scheme 1



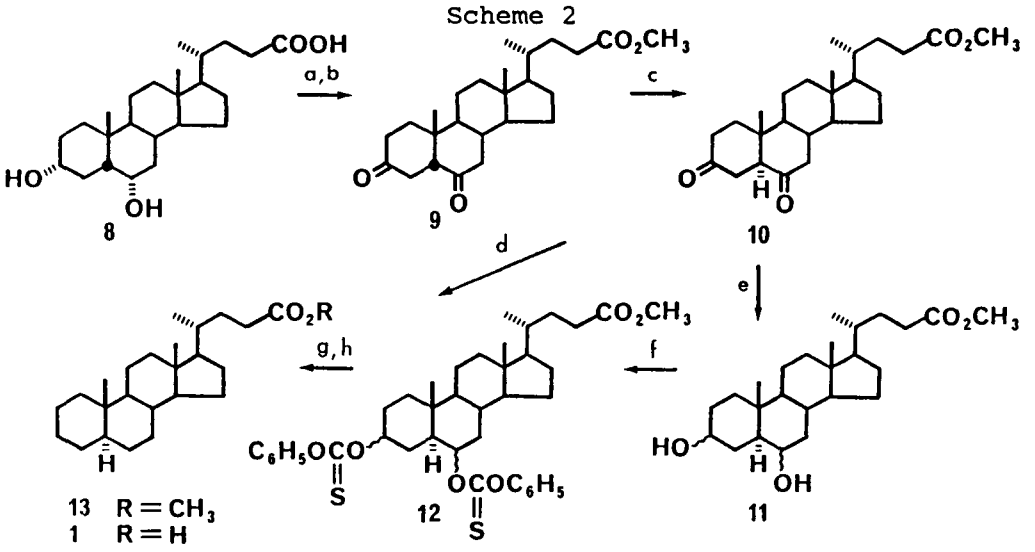
a) CH_3OH, H_3PO_4 b) PCC c) Br_2, p-TsOH (catalytic), DMF d) LiCl, DMF e) NaOH aqueous THF f) $Al(OiPr)_3$, 4-methyl-1-piperidone (ref 4) g) NaOH h) B_2H_6 followed by Ac_2O i) Li, NH_3 j) 1,2-ethanedithiol, $BF_3 \cdot Et_2O$

diborane followed by acetic anhydride provided only a 15% yield of the olefin 5. The lithium and ammonia reduction[5] of 4 gave a 30% yield of 3β-hydroxy-5α-cholan-24-oic acid (6), but the low yield and the need for additional steps to remove the 3β-hydroxy group made this route unattractive. The methyl copper-DIBAL-HMPA reduction[6] of the methyl ester of 4 gave a 1:1 mixture of methyl 3-oxo-5α- and 3-oxo-5β-cholan-24-oate in 59% yield according to a ^{13}C NMR analysis. The hydrogenation of the dithioketal 7 (or the methyl ester of 7) using either active Raney nickel[7,8] (600 psi, 10 hrs, 25°) or platinum[9]

(60 psi, 10 hrs, 25° in acetic acid) gave mostly unreacted starting material. The catalytic hydrogenation[10,11] of the enone 4 over platinum in acetic acid gave a 38% yield of a 1:2 mixture of the 5α- and 5β-cholan-24-oic acids according to a ^{13}C NMR analysis. Attempted side-chain degradation of 5α-cholestan-3-one to 3-oxo-5α-cholan-24-oic acid also failed.[12]

A successful synthesis of 1 from hyodeoxycholic acid (8) is shown in Scheme 2. Oxidation of the methyl ester of 8 and

Scheme 2



a) CH_3OH, H_3PO_4 b) PCC c) $NaOCH_3$, CH_3OH d) H_2NNH_2, $(HOCH_2CH_2)_2O$, 200° followed by aqueous NaOH e) $NaBH_4$, EtOH f) PhOC(S)Cl, Py g) n-Bu_3SnH h) NaOH, aq. CH_3OH

epimerization[13] of the 5β-stereocenter in 9 to the thermodynamically favored 5α-configuration in 10 provided direct access to the 5α-cholan-24-oic acid skeleton. The Wolff-Kishner reduction of the 3,6-diketo functionality in either the ester 10 (or the corresponding acid) provided a mixture[14] of 5α- and 5β-cholan-24-oic acid from which pure 1

was separated in poor yield. The preferred route to 1 from 10 involved the reduction of 10 with sodium borohydride to a mixture of diastereomeric diols 11, conversion of 11 to the bisthiocarbonate[15] 12, and reduction of 12 with tri-n-butyltin hydride to secure the methyl ester 13. Hydrolysis of 13 furnished the desired 5α-cholan-24-oic acid (1) in an overall yield of 52% from hyodeoxycholic acid (8).

EXPERIMENTAL SECTION

Infrared spectra were determined on a Beckman Microlab 600 or AX20 spectrometer. The abbreviation TF denotes thin film. NMR spectra were determined on a JEOL 270-MHz or Varian XL-200 spectrometer. Mass spectra were determined on VG ZAB mass spectrometer. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

3-Oxo-4-cholen-24-oic Acid (4) from Lithocholic Acid (2).- The procedure described by Ballini and Carotti[16] was repeated using 26.0 g of lithocholic acid, 160 mL of absolute methanol, and 16 mL of 85% phosphoric acid (reflux time: 42 hrs) to afford, after crystallization from aqueous methanol, 24.3 g (90%) of methyl lithocholate; mp. 125-126°, lit.[16] mp. 129-131°.

To 19.0 g of pyridinium chlorochromate in 300 mL of dichloromethane was added 25.3 g (58.9 mmol) of methyl lithocholate in 150 mL of dichloromethane. The mixture was stirred 16 hrs at which time an additional 6.30 g of pyridinium chlorochromate (total: 118 mmol, 2.0 eq) was added. The mixture was stirred an additional 6 hrs, diluted with 1.50 L of ether, and filtered through a Celite pad. The filtrate was washed successively with 1M hydrochloric acid solution, water, saturated sodium bicarbonate solution, and brine and, finally,

dried over anhydrous magnesium sulfate. The product was purified by chromatography on Merck silica gel 60 using 1:2 ethyl acetate-hexane to afford 21.0 g (92%) of methyl 3-oxo-5β-cholan-24-oate[17] IR (KBr) 1732, 1707 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.69 (s, 3, C-18 angular CH_3), 1.02 (s, 3, C-19 angular CH_3), 0.92 (d, J = 6.6 Hz, 3, C-21 CH_3), 3.66 (s, 3, OCH_3).

The procedure of Holysz[18] was repeated using 20.5 g (52.8 mmol) of methyl 3-oxo-5β-cholan-24-oate, 10.4 g (65.0 mmol, 1.2 eq) of bromine, and 425 mg of p-toluenesulfonic acid in 180 mL of N,N-dimethylformamide at 35-40° to afford crude α-bromoketone.

The crude product was dehydrobrominated using 6.73 g (158 mmol, 3.0 eq) of lithium chloride in 255 mL of N,N-dimethylformamide at 100° for 2.5 hrs to afford, after chromatography on Merck silica gel 60 using 1:2 ethyl acetate-hexane, 13.0 g (65%) of methyl 3-oxo-4-cholen-24-oate mp. 126.5-127.5°, lit.[19] mp. 126-127°; ^1H NMR ($CDCl_3$): δ 0.71 (s, 3, C-18 angular CH_3), 0.92 (d, J = 5.9 Hz, 3, C-21 CH_3), 1.18 (s, 3, C-19 angular CH_3), 3.67 (s, 3, OCH_3), 5.72 (s, 1, C-4 vinylic H).

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91
Found: C, 77.78; H, 9.94

To 8.68 g (22.5 mmol) of methyl 3-oxo-5-cholen-24-oate in 90 mL of 1:1 methanol-THF was added 45 mL of 5 M aqueous sodium hydroxide. The mixture was refluxed for 3 hrs. The product was concentrated, diluted with 20% dichloromethane-ether, and acidified with cold concentrated hydrochloric acid solution. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The crude product was recrystal-

lized from methanol-hexane to afford 5.59 g (67%) of 4 mp. 186-188°; lit.[20] mp. 185-186°; ^{1}H NMR ($CDCl_3$): δ 0.71 (s, 3, angular CH_3), 0.94 (d, J = 6.6 Hz, 3, C-21, CH_3), 1.18 (s, 3, C-19 angular CH_3, 5.74 (s, 1, C-4 vinylic H).

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74
Found: C, 77.40; H, 9.79

Methyl 3-Oxo-5-cholen-24-oate Dithioketal (7).- To 1.0 g (2.68 mmol) of 4 and 758 mg (8.06 mmol, 3.0 eq) of 1,2-ethanedithiol in 4 mL of dichloromethane was added 4 drops of distilled boron trifluoride etherate. The mixture was stirred for 9.5 hrs. The product was collected by filtration, washed with hexane and air-dried in a hood to afford 988 mg (82%) of 7 mp. 219.5-221°; ^{1}H NMR ($CDCl_3$): δ 0.68 (s, 3, C-18 angular CH_3), 0.92 (d, J = 6.5 Hz, 3, C-21 CH_3), 1.01 (s, 3, C-19 angular CH_3), 3.3-3.5 (m, 4, SCH_2CH_2S), 5.47 (m, 1, C-6 vinylic H).

Anal. Calcd. for $C_{26}H_{40}O_2S_2$: C, 69.61; H, 8.99
Found: C, 69.53; H, 9.04

Methyl Hyodeoxycholate.- The procedure described by Ballini and Carotti[16] was repeated using 15.7 g (40.0 mmol) of 8, 150 mL of absolute methanol, and 7 mL of 85% phosphoric acid (reflux time: 22 hrs) to afford 15.6 g (96%) of methyl hyodeoxycholate mp. 77-79°; IR (KBr) 3600-3100 (br OH), 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.64 (s, 3, C-18 angular CH_3), 0.90 (s, 3, C-19 angular CH_3), 0.91 (d, J = 6.6 Hz, 3, C-21 CH_3), 3.66 (s, 3, OCH_3); ^{13}C NMR ($CDCl_3$): δ 12.0, 18.2, 20.8, 23.6, 24.2, 28.2, 29.3, 30.1, 31.0, 31.1, 34.8, 35.4, 35.6, 35.9, 39.9, 40.0, 42.8, 48.5, 51.5, 56.0, 56.3, 68.0 (C-3 or C-6), 71.5

(C-3 or C-6), 174.7 ($\underline{C}O_2CH_3$). One signal among those listed above must represent two carbons.

Methyl 3,6-Dioxo-5α-cholan-24-ote (10).- To 15.6 g (38.6 mmol) of methyl hyodeoxycholate in 200 mL of anhydrous dichloromethane at 25° under a nitrogen atmosphere was added 33.1 g (150 mmol, 2.0 eq) of pyridinium chlorochromate. The mixture was stirred for 24 hrs and diluted with ether. The organic solution was decanted, washed with brine, and dried over anhydrous magnesium sulfate. The crude product was chromatographed on Merck silica gel 60 using 1:2 ethyl acetate-hexane to afford 13.4 g (87%) of a mixture of 9 and 10 as evidenced by the ^{13}C NMR spectrum ($CDCl_3$) which displayed four signals at δ 208.8, 209.0, 210.8, and 211.1 for the C-3 and C-6 carbonyl groups of 9 and 10. The principal product was presumably the C-5β epimer 9, and the ^1H NMR spectrum of the mixture displayed pronounced signals which we assigned to this epimer IR (KBr) 1738, 1713, 1691 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.70 (s, 3, C-18 angular CH_3), 0.94 (d, J=5.9 Hz, 3, C-21 CH_3), 0.96 (s, 3, C-19 angular CH_3), 3.67 (s, 3, OCH_3). No effort was made to separate the mixture of 9 and 10 which was used directly in the next step.

To a solution of sodium methoxide prepared from 3.00 g (130 mmol) of sodium and 450 mL of anhydrous methanol at 25° under a nitrogen atmosphere was added 13.2 g (32.8 mmol) of the mixture of diketones 9 and 10. After stirring for 2.5 hrs, the reaction was acidified with 6M hydrochloric acid solution, and extracted with ether. The combined ether extracts were washed with brine and dried over anhydrous magnes-

ium sulfate. The crude product, 13.2 g of 10, containing less than 5% of 9, was sufficiently pure to be used directly in the next step. A small sample of the mixture of 9 and 10 was purified by chromatography on Merck silica gel 60 PF254 in 1:2 ethyl acetate-hexane and recrystallized from ethyl acetate-hexane to afford pure 10 mp. 149-151°; IR (KBr) 1738, 1704 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.70 (s, 3, C-18 angular CH_3), 0.93 (d, J = 5.8 Hz, 3, C-21 CH_3), 0.96 (s, 3, C-19 angular CH_3), 3.66 (s, 3, OCH_3); ^{13}C NMR ($CDCl_3$): δ 12.0, 12.6, 18.2, 21.6, 23.9, 27.9, 30.9, 31.0, 35.3, 37.0, 37.4, 38.0, 38.1, 39.3, 41.2, 43.0, 46.6, 51.5, 53.4, 55.8, 56.5, 57.5, 174.6 ($\underline{C}O_2CH_3$), 209.0 (C-3 or C-6), 211.2 (C-3 or C-6).

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52
Found: C, 74.65; H, 9.60

Methyl 3,6-Dihydroxy-5α-cholan-24-oate (11).- To 2.00 g (4.97 mmol, 1.0 eq) of 10 in 250 mL of ethanol at 60° under a nitrogen atmosphere was added 440 mg (11.6 mmol, 4.0 eq) of sodium borohydride over a period of 20 min. The mixture was stirred at 25° for 4 hrs. The product was concentrated under reduced pressure, diluted with water and extracted with ether. The ether solutions were washed with brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to afford 1.98 g (98%) of semisolid 11 as a mixture of diastereomers at C-3 and C-6; IR (KBr) 3640-3120 (br OH), 1745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.69 (s, 3, C-18 angular CH_3), 0.92 (d, J = 5.9 Hz, 3, C-21 CH_3), 1.03 (s, 3, C-19 angular CH_3), 3.66 (s, 3, OCH_3).

Methyl 5α-Cholan-24-oate (13) from Diol 11.- To a solution of

1.90 g (4.68 mmol, 1.0 eq) of 11 in 50 mL of dichloromethane at 25° was added 2.94 g (37.2 mmol, 8.0 eq) of anhydrous pyridine and 2.26 g (12.0 mmol, 2.6 eq) of phenyl chlorothionocarbonate under a nitrogen atmosphere. The mixture was stirred for 12 hrs. The solvent was evaporated, and the product was chromatographed on Macherey-Nagel silica gel 60 using 1:5 ether-hexane to afford 2.70 g (87%) of semisolid 12 as a mixture of diastereomers at C-3 and C-6; IR (KBr) 1740, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.70 (s, 3, C-18 angular CH_3), 0.84 (s, 3, C-19 angular CH_3), 0.93 (d, J=6 Hz, 3, C-21 CH_3), 3.67 (s, 3, OCH_3), 7.06-7.50 (m, 10, aromatic H).

Anal. Calcd. for $C_{39}H_{50}O_6S_2$: C, 68.99; H, 7.42
Found: C, 69.13; H, 7.44

The procedure of Robins[15b] was repeated using 678 mg (1.00 mmol, 1.0 eq) of 12 and 1.46 g (5.02 mmol, 5.0 eq) of tri-n-butyltin hydride in 17 mL of toluene to afford, after chromatography on Macherey-Nagel silica gel 60 using 1:9 ethyl acetate-hexane, 287 mg (78%) of 13; mp. 90-91°, lit.[11b] mp. 92-94°); IR (KBr) 1737 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.64 (s, 3, C-18 angular CH_3), 0.77 (s, 3, C-19 angular CH_3), 0.91 (d, J = 6.2 Hz, 3, C-21 CH_3), 3.66 (s, 3, OCH_3).

Anal. Calcd. for $C_{25}H_{42}O_2$: C, 80.16; H, 11.30
Found: C, 80.28; H, 11.33

5α-Cholan-24-oic acid (1) from Ester 13.- To 325 mg (0.869 mmol, 1.0 eq) of 13 was added 100 mg (2.50 mmol, 2.9 eq) of sodium hydroxide in 10 mL of methanol and 2 mL of water. The mixture was refluxed for 2 hrs, and the methanol was evaporated under reduced pressure. The product was diluted with

water, acidified with 1M hydrochloric acid solution and extracted with ethyl acetate. The combined extracts were washed with brine and dried over anhydrous magnesium sulfate. The product was crystallized from methanol to afford 294 mg (94%) of 1 mp.[19] 168-169°, lit.[13a] mp. 162°, lit.[9] mp. 165-166°, lit.[8b] mp. 172-173°; IR (KBr) 3400-2500 (broad), 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.65 (s, 3, C-18 angular CH_3), 0.77 (s, 3, C-19 angular CH_3), 0.92 (d, J = 6.6 Hz, 3, C-21 CH_3); ^{13}C NMR ($CDCl_3$): δ 12.1 (C-18 or C-19), 12.2 (C-18 or C-19), 18.2 (C-21), 20.8 (C-11), 22.2 (C-2), 24.2 (C-15), 26.9 (C-3), 28.1 (C-16), 29.1 (coincident C-4 and C-6), 30.8 (C-22 or C-23), 31.0 (C-22 or C-23), 32.2 (C-7), 35.3 (C-20), 35.5 (C-8), 36.2 (C-10), 38.7 (C-1), 40.1 (C-12), 42.7 (C-13), 47.0 (C-5), 54.7 (C-9), 55.9 (C-17), 56.6 (C-14), 180.7 (C-24 $\underline{C}O_2H$).[22] For comparison, we also determined the ^{13}C NMR ($CDCl_3$) spectrum of 5β-cholan-24-oic acid which showed C-5 at δ 43.7.

Anal. Calcd. for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18
Found: C, 80.00; H, 11.22

5α-Cholan-24-oic acid (1) from Diketone 10.- To a solution of 4.55 g (199 mmol) of sodium in 200 mL of 2-hydroxyethyl ether was added 40 mL of anhydrous hydrazine and 3.78 g (9.39 mol) of 10. The temperature was slowly raised to 200°, and the reaction was stirred at 200° for 20 hrs. The temperature was lowered to 150°, 75 mL of water was added, and the reaction was stirred for an additional 5 hrs in order to hydrolyze any hydrazide formed from the methyl ester. After cooling to 25°, the reaction was acidified with concentrated hydrochloric acid solution and extracted with two 300 mL portions of ether. The

combined ether extracts were washed with three 100 mL portions of brine and dried over anhydrous magnesium sulfate. The crude product was chromatographed on Macherey Nagel silica gel F254 using 1:5:10 methanol-ethyl acetate-hexane to afford 825 mg (24%) of 1. The chromatographed product was recrystallized from ether-hexane to remove a small amount of 5β-isomer impurity detected by ^{13}C NMR analysis (vide supra for assignments) and to provide pure 1.

Acknowledgement.- We thank Dr. V. Van Rheenan of the Upjohn Company for a sample of 3 and Charlene Haertzen for technical assistance.

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(Received July 7, 1986; in revised form December 12, 1986)