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Stereoselective synthesis of pentacyclic steroids functionalized at C-11

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ABSTRACT

We set out to describe an efficient and versatile method for preparing pentacyclic steroids diversely substituted at C-11 from cholic acid, *via* a stereoselective epoxidation and the epoxide opening as the key steps. The characteristic ^{1}H and ^{13}C NMR spectroscopic features of the synthesized compounds are reported.

1. Introduction

Steroids represent an important class of natural products due to their high ability to penetrate cells and bind to nuclear and membrane receptors. The steroid system, selected by the evolutionary process to perform some of the most fundamental biological functions, has not only inspired biochemists and endocrinologists, but has also become the basis of many important discoveries in organic chemistry.

The fact that minor changes in steroid structures can cause extensive changes in biological activity has long intrigued medicinal chemists. Naturally occurring steroid nuclei have been modified in several ways with the aim of finding more active compounds, free from undesirable or harmful side effects, and of recognizing the structural and stereochemical features required for the display of specific, selective physiological activity.

Bile acids (BA) have been the subject of numerous pharmacological studies. Their amphiphilic character generally increases cell membrane permeability. As they enhance the absorption of hydrophobic drugs, they can be used to improve the delivery of drugs that specifically target the liver [1]. Some bile acid derivatives are potent antibiotics against Gram-negative bacteria [2,3].

Otherwise, pentacyclic steroids constitute an important class of steroids. There are many examples of pentacyclic steroidal derivatives of pharmacological and biological importance [4,5]. Pentacyclic steroids obtained by fusion of a carbocyclic ring such as benzene or cyclohexane or cyclopentane to the steroid nucleus or pentacyclic steroids derived by the fusion of a carbocyclic ring to a heterosteroid skeleton are known to exhibit interesting and diverse biological properties [6–9].

So, it would be interesting to introduce a new ring and a new function at the C-11 position of the steroidal skeleton which is a key position from a biological point of view [10–14], in order to obtain a new class of steroids. We report herein an efficient stereoselective synthesis of pentacyclic steroids from cholic acid (Scheme 1). We show that we can introduce by our method not only an amine but also a thiol function or a selenium at the C-11 position of the steroidal skeleton. We report here the full details of these syntheses.

2. Experimental section

All reactions were run under argon in oven-dried glassware. ^{1}H and ^{13}C NMR spectra are recorded at 200 or 400 and 50 and 100 MHz respectively, in $CDCl_3$ solutions. Chemical shift (δ) are reported in ppm with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. Flash chromatography was performed on silica gel (Merk 60 F_{254}) and TLC on silica gel. Dichloromethane was distilled from P_2O_5 and tetrahydrofuran (THF) over sodium/benzophenone.

Compounds **4** and **5** were prepared according to the previously described procedure [15]. The nomenclature used for the steroids is not the nomenclature used by chemical abstracts [16,17].

2.1. Methyl 3α,7α-diacetylcholan-11-enate (5)

A mixture of anhydrous hexamethylphosphoric triamide (100 mL), potassium acetate (40 g, 0.4 mmol) and methyl 3,7-

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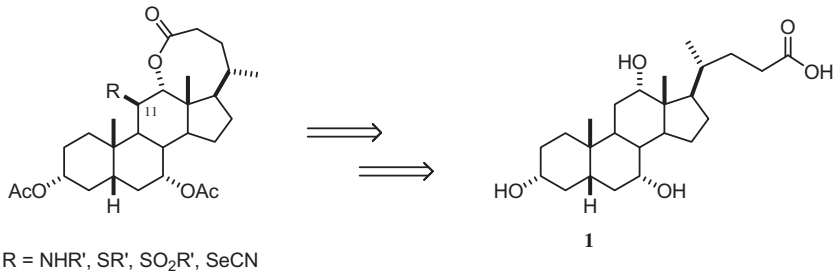


Scheme 1. Retrosynthetic pathway.

diacetyl-12-mesylcholate **4** (10 g, 17 mmol) was heated at 100 °C under argon for 48 h. The reaction mixture, which became slightly yellow and viscous, was poured into water and ice (1 L). The white solid product that precipited was allowed to coagulate and solidify in the refrigerator for at least 3 h before filtration. The solid collected was washed thoroughly with water to give the crude product. This latter was recrystallized slowly from methanol and water to give pure methyl 3,7-diacetylchol-11-enate **5** (6.7 g, 80% yield) as colorless needles. mp = 139–141 °C; ^{1}H NMR ($CDCl_3$) 6.15 (dd, J = 2.8, 10.1 Hz, 1H, H-11), 5.45 (dd, J = 1.7, 11.8 Hz, 1H, H-12), 4.96 (m, 1H, H-3β), 4.59 (m, 1H, H-7β), 3.65 (s, 3H, OCH_3), 3.16 (d, J = 4.02 Hz, 1H, H-11), 2.72 (m, 1H, H-23), 2.05 (s, 3H, CH_3C═O), 2.01 (s, 3H, CH_3C═O), 1.00 (d, J = 6.2 Hz, 3H, H-21), 0.88 (s, 3H, H-19), 0.72 (s, 3H, H-18); ^{13}C NMR ($CDCl_3$) 174.6, 170.6, 170.4, 139.1, 135.2, 73.9, 71.3, 62.6, 51.5, 49.2, 45.0, 40.2, 36.6, 36.3, 35.9, 35.2, 32.6, 31.8, 30.9, 30.8, 28.4, 26.7, 23.0, 22.4, 21.6, 21.6, 21.5, 18.3, 16.7.

2.2. Methyl 3α,7α-diacetyl-11α,12α-epoxy-5β-cholan-24-oate (6)

Methyl 3α,7α-diacetylchol-11-enate **5** (1 g, 2 mmol) was dissolved in CH_2Cl_2 (15 mL), under argon. The solution was cooled at 0 °C and MCPBA (380 mg, 2.2 mmol) was added. After stirring at room temperature for 24 h, the mixture was hydrolyzed with a saturated solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate: 4/6), to afford 930 mg (92% yield) of epoxide **6**. mp = 166 °C; IR (neat) 1305, 1220, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$) 4.85 (m, 1H, H-3β), 4.58 (m, 1H, H-7β), 3.65 (s, 3H, OCH_3), 3.16 (d, J = 4.02 Hz, 1H, H-11), 2.99 (d, J = 4.15 Hz, 1H, H-12), 2.04 (s, 3H, CH_3C═O), 2.02 (s, 3H, CH_3C═O), 1.03 (d, J = 6.0 Hz, 3H, H-21), 0.99 (s, 3H, H-19), 0.78 (s, 3H, H-18); ^{13}C NMR ($CDCl_3$) 174.6, 170.8, 170.4, 76.3, 73.6, 70.7, 60.6, 53.3, 51.5, 50.2, 43.7, 42.1, 40.5, 35.0, 34.9, 34.8, 34.7, 34.3, 31.6, 30.9, 30.6, 27.2, 26.8, 23.5, 21.7, 21.6, 21.4, 18.3, 11.9. HRMS Calcd for $C_{29}H_{44}O_7$ 504.3087, found 504.3092.

2.3. General procedure for the epoxide ring opening

To a solution of epoxide **6** (0.5 mmol) in anhydrous EtOH/toluene (1/1) (15 mL) an amine or a thiol (2.5 mmol) was added dropwise over a period of 5 min under an argon atmosphere. The solution was heated at reflux for 24 h. The solvent was then evaporated and the product dissolved in dichloromethane (20 mL). The mixture was hydrolyzed with a saturated solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (typically eluting with CH_2Cl_2: MeOH, 95:5 for **7** or petroleum ether: diethyl ether, 9:1 to 7:3 for **8**) to give the corresponding 11-amino lactone **7** or 11-thio lactone **8**.

2.4. Methyl 3α,7α-diacetyl-11β-phenylamino-12α-oxo-5β,17β-cholan-24-one (7a)

Yield 235 mg (81%). Oil. IR (neat) 3509, 3236, 1736, 1606, 1511 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 5H), 5.29 (s, 2H, NCH_2Ph), 4.85 (m, 1H, H-3β), 4.42 (d, J = 4.1 Hz, 1H, H-12), 3.51 (m, 1H, H-7β), 3.06 (dd, J = 3.6, 3.9 Hz, 1H, H-11), 2.03 (s, 3H, CH_3C═O), 2.02 (s, 3H, CH_3C═O), 1.04 (d, J = 5.4 Hz, 3H, H-21), 0.98 (s, 3H, H-19), 0.77 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 170.6, 170.5, 138.5, 128.7 (2C), 127.8 (2C), 127.5, 92.1, 71.8, 71.0, 53.4, 53.5, 50.1, 43.8, 43.7, 43.6, 42.2, 40.7, 39.4, 35.1, 35.0, 34.9, 34.8, 34.4, 33.3, 31.7, 31.5, 30.8, 23.6, 21.6, 21.5, 18.4, 11.9. HRMS Calcd. for $C_{35}H_{49}NO_6$ 579.356, found 579.3564.

2.5. Methyl 3α,7α-diacetyl-11β-(p-methoxyphenyl)amino-12α-oxo-5β,17β-cholan-24-one (7b)

Yield 200 mg (65%). Oil. IR (neat) 3447, 2940, 1732, 1608 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98 (d, J = 8.5 Hz, 2H), 6.62 (d, J = 8.5 Hz, 2H), 5.28 (s, 2H, NCH_2Ph), 4.82 (m, 1H, H-3β), 4.36 (d, J = 4.0 Hz, 1H, H-12), 3.76 (s, 3H, OCH_3), 3.49 (m, 1H, H-7β), 3.12 (dd, J = 3.4, 3.8 Hz, 1H, H-11), 2.01 (s, 3H, CH_3C═O), 1.98 (s, 3H, CH_3C═O), 1.02 (d, J = 5.7 Hz, 3H, H-21), 0.97 (s, 3H, H-19), 0.75 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 170.6, 170.5, 160.5, 129.9 (2C), 128.8, 115.6 (2C), 91.8, 71.3, 70.9, 56.2, 53.1, 52.9, 50.4, 43.9, 43.6, 42.9, 42.2, 40.6, 39.6, 35.7, 35.2, 34.6, 34.2, 33.8, 32.9, 31.6, 31.1, 29.8, 23.7, 21.2, 20.8, 17.9, 11.7. HRMS Calcd. for $C_{36}H_{51}NO_7$ 609.3666, found 609.3671.

2.6. Methyl 3α,7α-diacetyl-11β-phenylamino-12α-oxo-5β,17β-cholan-24-one (7c)

Yield 250 mg (88%). Oil. IR (neat) 3410, 2960, 1728, 1362, 1064 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (m, 5H), 4.48 (d, J = 3.9 Hz, 1H, H-12), 4.32 (m, 1H, H-3β), 3.62 (m, 1H, H-7β), 3.18 (dd, J = 3.1, 4.0 Hz, 1H, H-11), 2.04 (s, 3H, CH_3C═O), 2.02 (s, 3H, CH_3C═O), 1.06 (d, J = 6.1 Hz, 3H, H-21), 0.96 (s, 3H, H-19), 0.76 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 170.3, 170.2, 148.5, 129.7 (2C), 118.2, 114.6 (2C), 91.4, 72.0, 71.7, 50.1, 48.9, 44.7, 44.6, 43.2, 39.2, 35.4, 35.1, 34.6, 34.0, 33.8, 31.7, 31.2, 30.6, 28.4, 27.6, 27.1, 23.8, 21.7, 21.3, 18.3, 11.8. HRMS Calcd. for $C_{34}H_{47}NO_6$ 565.3403, found 565.3408.

2.7. Methyl 3α,7α-diacetyl-11β-(4-methylphenyl)amino-12α-oxo-5β,17β-cholan-24-one (7d)

Yield 195 mg (67%). Oil. IR (neat) 3386, 1713, 820 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 8.3 Hz, 2H), 4.52 (d, J = 3.8 Hz, 1H, H-12), 4.48 (m, 1H, H-3β), 3.54 (m, 1H, H-7β), 3.12 (dd, J = 3.6, 4.1 Hz, 1H, H-11), 2.38 (s, 3H, CH_3Ph), 2.03 (s, 3H, CH_3C═O), 2.01 (s, 3H, CH_3C═O), 1.01 (d, J = 6.1 Hz, 3H, H-21), 0.97 (s, 3H, H-19), 0.82 (s, 3H, H-18); ^{13}C NMR

(75 MHz, $CDCl_3$): δ = 173.6, 170.6, 170.4, 138.9, 133.1, 127.6 (2C), 127.1 (2C), 90.6, 73.6, 72.7, 47.9, 47.2, 45.2, 44.7, 39.6, 38.2, 35.7, 35.3, 34.2, 34.2, 33.8, 31.6, 31.7, 31.2, 28.4, 27.6, 27.2, 24.3, 24.0, 21.4, 21.1, 17.9, 11.4. HRMS Calcd. for $C_{35}H_{49}NO_6$ 579,356 found 579.3564.

2.8. Methyl 3α,7α-diacetyl-11β-(4-methoxyphenyl)amino-12α-oxo-5β,17β-cholan-24-one (7e)

Yield 190 mg (64%). Oil. IR (neat) 3428, 2970, 1718, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.66 (d, J = 8.1 Hz, 2H), 6.28 (d, J = 3.8 Hz, 2H), 4.56 (d, J = 6.4 Hz, 1H, H-12), 4.39 (m, 1H, H-3β), 3.74 (s, 3H, OCH_3), 3.48 (m, 1H, H-7β), 3.16 (dd, J = 3.6, 4.1 Hz, 1H, H-11), 2.02 (s, 3H, CH_3C═O), 2.01 (s, 3H, CH_3C═O), 0.99 (d, J = 6.4 Hz, 3H, H-21), 0.92 (s, 3H, H-19), 0.79 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 170.8, 170.3, 149.2, 139.7, 117.4 (2C), 114.8 (2C), 90.6, 72.9, 71.6, 55.8, 49.9, 47.7, 47.4, 44.8, 38.2, 37.8, 35.6, 35.2, 34.7, 34.1, 33.9, 33.5, 31.7, 31.6, 30.6, 28.4, 27.9, 27.1, 21.6, 21.2, 18.7, 11.6. HRMS Calcd. for $C_{35}H_{49}NO_7$ 595.3509, found 595.3514.

2.9. Methyl 3α,7α-diacetyl-11β-(4-fluorophenyl)amino-12α-oxo-5β,17β-cholan-24-one (7f)

Yield 245 mg (83%). Oil. IR (neat) 3435, 2990, 1712, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.62 (m, 2H), 6.31 (m, 2H), 4.39 (d, J = 3.9 Hz, 1H, H-12), 4.09 (m, 1H, H-3β), 3.46 (m, 1H, H-7β), 3.07 (dd, J = 3.5, 4.1 Hz, 1H, H-11), 2.02 (s, 3H, CH_3C═O), 2.01 (s, 3H, CH_3C═O), 1.04 (d, J = 6.3 Hz, 3H, H-21), 0.99 (s, 3H, H-19), 0.77 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 170.6, 170.1, 153.9 ($J_{C,F}$ = 243.2 Hz), 146.4, 119.2 (2C, $J_{C,F}$ = 21 Hz), 117.6 (2C, $J_{C,F}$ = 6.9 Hz), 91.1, 75.3, 73.9, 50.6, 47.9, 47.5, 44.6, 37.6, 35.4, 34.9, 34.2, 33.9, 33.2, 31.0, 30.9, 30.3, 28.2, 27.3, 27.1, 23.8, 21.6, 21.1, 18.6, 11.4. HRMS Calcd. for $C_{34}H_{46}FNO_6$ 583.3309, found 583.3313.

2.10. Methyl 3α,7α-diacetyl-11β-(4-trifluoromethyl)phenylamino-12α-oxo-5β,17β-cholan-24-one (7g)

Yield 230 mg (72%). Oil. IR (neat) 3425, 1712, 1180, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, J = 7.9 Hz, 2H), 6.42 (d, J = 8.1 Hz, 2H), 4.52 (d, J = 3.9 Hz, 1H, H-12), 4.17 (m, 1H, H-3β), 3.48 (m, 1H, H-7β), 3.13 (dd, J = 3.7, 4.0 Hz, 1H, H-11), 2.02 (s, 3H, CH_3C═O), 2.01 (s, 3H, CH_3C═O), 1.12 (d, J = 6.4 Hz, 3H, H-21), 0.87 (s, 3H, H-19), 0.79 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 170.6, 170.1, 151.6, 126.7 (2C, $J_{C,F}$ = 36.8 Hz), 124.6, 119.1 ($J_{C,F}$ = 264.3 Hz), 114.2 (2C, $J_{C,F}$ = 4.2 Hz), 92.0, 74.9, 73.6, 50.6, 47.9, 47.6, 44.2, 43.6, 38.9, 35.7, 35.2, 34.2, 33.9, 32.8, 31.7, 31.0, 30.1, 28.7, 27.6, 27.2, 24.3, 21.3, 21.0, 18.1, 11.3. HRMS Calcd. for $C_{35}H_{46}F_3NO_6$ 633.3277, found 633.3283.

2.11. Methyl 3α,7α-diacetyl-11β-propylamino-12α-oxo-5β,17β-cholan-24-one (7h)

Yield 185 mg (70%). Oil. IR (neat) 3431, 1721, 1264, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.39 (d, J = 3.8 Hz, 1H, H-12), 4.12 (m, 1H, H-3β), 3.39 (m, 1H, H-7β), 3.11 (dd, J = 3.9, 4.1 Hz, 1H, H-11), 2.63 (m, 2H, CH_2NH), 2.03 (s, 3H, CH_3C═O), 2.01 (s, 3H, CH_3C═O), 1.19 (d, J = 6.4 Hz, 3H, H-21), 1.02 (t, J = 6.5 Hz, 3H, CH_3), 0.98 (s, 3H, H-19), 0.76 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 170.6, 170.5, 89.8, 72.9, 71.8, 51.6, 50.3, 47.8, 45.7, 44.9, 43.1, 38.9, 35.2, 34.9, 34.4, 33.8, 33.6, 31.5, 31.0, 30.8, 28.6, 27.9, 27.1, 24.3, 23.7, 21.6, 21.2, 18.6, 16.2, 11.7. HRMS Calcd. for $C_{31}H_{49}NO_6$ 531.356, found 531.3564.

2.12. Methyl 3α,7α-diacetyl-11β-butylamino-12α-oxo-5β,17β-cholan-24-one (7i)

Yield 205 mg (75%). Oil. IR (neat) 3434, 1716, 1264, 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.42 (d, J = 3.7 Hz, 1H, H-12), 4.19 (m, 1H, H-3β), 3.43 (m, 1H, H-7β), 3.16 (dd, J = 3.6, 3.9 Hz, 1H, H-11), 2.66 (m, 2H, CH_2NH), 2.02 (s, 3H, CH_3C═O), 2.01 (s, 3H, CH_3C═O), 1.16 (d, J = 6.3 Hz, 3H, H-21), 1.06 (t, J = 6.4 Hz, 3H, CH_3) 0.92 (s, 3H, H-19), 0.77 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 170.9, 170.3, 90.2, 74.6, 73.1, 51.2, 50.1, 47.6, 45.9, 45.1, 43.6, 38.7, 35.4, 34.9, 34.6, 33.6, 32.9, 31.4, 31.1, 30.7, 28.6, 27.5, 27.2, 24.1, 23.4, 21.4, 21.1, 20.6, 18.4, 15.7, 11.6. HRMS Calcd. for $C_{32}H_{51}NO_6$ 545.3716, found 545.3719.

2.13. Methyl 3α,7α-diacetyl-11β-naphthylamino-12α-oxo-5β,17β-cholan-24-one (7j)

Yield 205 mg (66%). Oil. IR (neat) 3450, 2929, 1716, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (m, 3H), 7.28 (m, 3H), 6.59 (m, 1H), 4.39 (d, J = 4.0 Hz, 1H, H-12), 4.32 (m, 1H, H-3β), 3.62 (m, 1H, H-7β), 3.06 (dd, J = 3.7, 3.9 Hz, 1H, H-11), 2.04 (s, 3H, CH_3C═O), 2.02 (s, 3H, CH_3C═O), 1.12 (d, J = 6.3 Hz, 3H, H-21), 0.93 (s, 3H, H-19), 0.72 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 170.6, 170.1, 147.9, 134.8, 129.2, 128.7, 126.9, 126.6, 125.4, 121.9, 118.8, 110.7, 90.7, 76.5, 73.7, 50.4, 48.1, 47.7, 44.7, 42.9, 35.7, 34.1, 33.9, 33.8, 33.1, 32.8, 31.6, 31.0, 30.5, 27.9, 27.6, 27.3, 24.2, 21.5, 21.1, 18.8, 11.4. HRMS Calcd. for $C_{38}H_{49}NO_6$ 615.356, found 615.3564.

2.14. Methyl 3α,7α-diacetyl-11β-benzylsulfanyl-12α-oxo-5β,17β-cholan-24-one (8a)

Yield 215 mg (72%). Oil. IR (neat) 3448, 1715, 1607, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.12 (m, 5H), 4.59 (m, 1H, H-3β), 4.23 (d, J = 4.1 Hz, 1H, H-12), 3.46 (m, 1H, H-7β), 3.18 (s, 2H, SCH_2Ph), 3.02 (dd, J = 3.6, 3.9 Hz, 1H, H-11), 2.04 (s, 3H, CH_3C═O), 2.01 (s, 3H, CH_3C═O), 1.16 (d, J = 5.6 Hz, 3H, H-21), 0.98 (s, 3H, H-19), 0.76 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 170.8, 170.3, 137.9, 128.8 (2C), 127.9 (2C), 126.9, 90.8, 76.8, 73.2, 51.5, 48.8, 44.3, 43.2, 43.6, 41.9, 40.2, 37.9, 35.4, 35.0, 34.7, 34.2, 33.9, 33.3, 32.4, 31.6, 31.0, 30.7, 22.9, 21.7, 21.2, 18.1, 11.1. HRMS Calcd. for $C_{35}H_{48}O_6S$ 596.3172, found 596.3176.

2.15. Methyl 3α,7α-diacetyl-11β-(p-methoxybenzyl)sulfanyl-12α-oxo-5β,17β-cholan-24-one (8b)

Yield 195 mg (62%). Oil. IR (neat) 3418, 1726, 1492, 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.02 (d, J = 8.6 Hz, 2H), 6.72 (d, J = 8.1 Hz, 2H), 4.47 (m, 1H, H-3β), 4.19 (d, J = 3.9 Hz, 1H, H-12), 3.78 (s, 3H, OCH_3), 3.42 (m, 1H, H-7β), 3.29 (s, 2H, SCH_2Ph), 3.09 (dd, J = 3.6, 4.0 Hz, 1H, H-11), 2.01 (s, 3H, CH_3C═O), 2.00 (s, 3H, CH_3C═O), 1.04 (s, 3H, H-19), 1.01 (d, J = 6.1 Hz, 3H, H-21), 0.79 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 170.3, 170.5, 158.8, 129.8 (2C), 128.47, 115.1 (2C), 91.8, 75.8, 73.1, 55.2, 51.9, 48.4, 44.5, 43.2, 42.7, 42.0, 40.3, 38.6, 35.6, 35.1, 34.2, 34.0, 33.7, 33.2, 32.5, 31.3, 31.1, 28.8, 23.6, 21.2, 20.9, 17.8, 11.6. HRMS Calcd. for $C_{36}H_{50}O_7S$ 626.3277, found 626.3281.

2.16. Methyl 3α,7α-diacetyl-11β-phenylsulfanyl-12α-oxo-5β,17β-cholan-24-one (8c)

Yield 250 mg (82%). Oil. IR (neat) 3420, 1716, 905, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32 (m, 5H), 4.53 (d, J = 4.1 Hz, 1H, H-12), 4.39 (m, 1H, H-3β), 3.69 (m, 1H, H-7β), 3.04 (dd, J = 3.5, 3.8 Hz, 1H, H-11), 2.05 (s, 3H, CH_3C═O), 2.03 (s, 3H, CH_3C═O), 1.09 (d, J = 6.2 Hz, 3H, H-21), 0.94 (s, 3H, H-19), 0.72 (s, 3H, H-18); ^{13}C

NMR (75 MHz, $CDCl_3$): δ = 175.1, 170.7, 170.4, 136.5, 129.5 (2C), 126.2 (2C), 124.9, 90.9, 76.1, 73.9, 49.9, 47.8, 44.7, 44.5, 43.3, 38.7, 36.0, 34.8, 34.3, 33.9, 33.7, 31.2, 31.0, 30.4, 29.4, 27.6, 26.4, 23.5, 21.6, 21.3, 17.9, 10.9. HRMS Calcd. for $C_{34}H_{46}O_6S$ 582.3015, found 582.3020.

2.17. Methyl 3α,7α-diacetyl-11β-(4-methylphenyl)sulfanyl-12α-oxo-5β,17β-cholan-24-one (8d)

Yield 190 mg (64%). Oil. IR (neat) 3353, 2976, 1712, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.12 (d, J = 7.9 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 4.59 (d, J = 4.0 Hz, 1H, H-12), 4.49 (m, 1H, H-3β), 3.57 (m, 1H, H-7β), 3.09 (dd, J = 3.9, 4.1 Hz, 1H, H-11), 2.41 (s, 3H, CH_3Ph), 2.03 (s, 3H, CH_3C=O), 2.00 (s, 3H, CH_3C=O), 1.11 (d, J = 6.1 Hz, 3H, H-21), 0.97 (s, 3H, H-19), 0.86 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 170.9, 170.1, 136.8, 134.0, 128.6 (2C), 125.9 (2C), 90.5, 74.6, 73.2, 49.7, 47.7, 44.3, 43.7, 40.3, 37.2, 35.6, 35.3, 34.7, 34.2, 33.7, 31.9, 31.0, 29.7, 28.4, 27.6, 27.2, 24.6, 23.9, 21.4, 20.9, 17.7, 11.6. HRMS Calcd. for $C_{35}H_{48}O_6S$ 596.3172 found 596.3177.

2.18. Methyl 3α,7α-diacetyl-11β-(4-methoxyphenyl)sulfanyl-12α-oxo-5β,17β-cholan-24-one (8e)

Yield 200 mg (65%). Oil. IR (neat) 3455, 2965, 1718, 1609, 1502 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.98 (d, J = 8.3 Hz, 2H), 6.59 (d, J = 8.1 Hz, 2H), 4.52 (d, J = 4.1 Hz, 1H, H-12), 4.31 (m, 1H, H-3β), 3.76 (s, 3H, OCH_3), 3.50 (m, 1H, H-7β), 3.17 (dd, J = 3.8, 4.1 Hz, 1H, H-11), 2.02 (s, 3H, CH_3C=O), 2.00 (s, 3H, CH_3C=O), 1.02 (d, J = 6.4 Hz, 3H, H-21), 0.89 (s, 3H, H-19), 0.78 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 170.4, 170.2, 157.9, 128.7, 127.8 (2C), 115.6 (2C), 90.1, 76.1, 73.4, 56.3, 50.6, 47.3, 41.7, 40.4, 37.8, 36.5, 35.4, 34.9, 34.7, 34.2, 33.5, 32.9, 31.8, 31.2, 29.6, 28.7, 27.5, 27.1, 21.5, 20.9, 17.6, 11.3. HRMS Calcd. for $C_{35}H_{48}O_7S$ 612.3121, found 612.3126.

2.19. Methyl 3α,7α-diacetyl-11β-(4-fluorophenyl)sulfanyl-12α-oxo-5β,17β-cholan-24-one (8f)

Yield 235 mg (78%). Oil. IR (neat) 3429, 2950, 1718, 1606, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.09 (m, 2H), 6.83 (m, 2H), 4.33 (d, J = 4.0 Hz, 1H, H-12), 4.05 (m, 1H, H-3β), 3.48 (m, 1H, H-7β), 3.02 (dd, J = 8.6, 3.9 Hz, 1H, H-11), 2.03 (s, 3H, CH_3C=O), 2.01 (s, 3H, CH_3C=O), 1.06 (d, J = 3.4 Hz, 3H, H-21), 0.83 (s, 3H, H-19), 0.72 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 170.7, 170.4, 158.3 ($J_{C,F}$ = 240.0 Hz), 133.8, 127.9 (2C, $J_{C,F}$ = 6.8 Hz), 115.2 (2C, $J_{C,F}$ = 21.0 Hz), 89.9, 76.6, 73.7, 51.3, 49.7, 45.6, 42.8, 40.9, 37.2, 37.8, 35.3, 35.1, 34.6, 34.0, 33.7, 33.4, 31.5, 30.9, 28.6, 28.4, 27.9, 27.2, 21.9, 21.0, 17.7, 11.2. HRMS Calcd. for $C_{34}H_{45}FO_6S$ 600.2921, found 600.2925.

2.20. Methyl 3α,7α-diacetyl-11β-propylsulfanyl-12α-oxo-5β,17β-cholan-24-one (8g)

Yield 180 mg (66%). Oil. IR (neat) 3420, 2981, 1721, 1370, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.27 (d, J = 3.9 Hz, 1H, H-12), 3.96 (m, 1H, H-3β), 3.31 (m, 1H, H-7β), 3.04 (dd, J = 3.7, 3.9 Hz, 1H, H-11), 2.57 (m, 2H, CH_2S), 2.04 (s, 3H, CH_3C=O), 2.02 (s, 3H, CH_3C=O), 1.12 (d, J = 6.4 Hz, 3H, H-21), 0.99 (t, J = 6.5 Hz, 3H, CH_3), 0.89 (s, 3H, H-19), 0.74 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 170.8, 170.1, 89.9, 74.9, 72.1, 52.1, 50.6, 48.2, 44.9, 43.7, 42.1, 38.7, 36.4, 34.3, 34.0, 33.7, 33.2, 31.2, 31.0, 30.7, 28.4, 27.6, 26.9, 25.3, 23.4, 21.6, 21.3, 18.3, 15.2, 11.2. HRMS Calcd. for $C_{31}H_{48}O_6S$ 548.3172, found 548.3179.

2.21. Methyl 3α,7α-diacetyl-11β-(2-methyl)-butylsulfanyl-12α-oxo-5β,17β-cholan-24-one (8h)

Yield 180 mg (62%). Oil. IR (neat) 3422, 2984, 1712, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.33 (d, J = 4.1 Hz, 1H, H-12), 3.91 (m, 1H, H-3β), 3.42 (m, 1H, H-7β), 3.08 (dd, J = 3.8, 4.0 Hz, 1H, H-11), 2.62 (m, 2H, CH_2S), 2.03 (s, 3H, CH_3C=O), 2.00 (s, 3H, CH_3C=O), 1.16 (d, J = 6.0 Hz, 3H, CH_3CH), 1.09 (d, J = 6.4 Hz, 3H, H-21), 1.01 (t, J = 6.2 Hz, 3H, CH_3CH_2), 0.86 (s, 3H, H-19), 0.72 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 170.6, 170.2, 90.7 (90.6), 75.3 (75.1), 73.7 (73.2), 51.6, 50.4 (50.2), 47.7 (47.4), 45.6, 44.4 (44.0), 43.7 (43.5), 37.7 (37.3), 36.2 (36.0), 34.7, 34.1 (34.0), 33.8 (33.5), 32.7 (32.4), 31.7 (31.3), 31.2, 29.9 (29.6), 28.2 (28.0), 27.7, 27.1 (27.4), 24.9, 23.2, 21.4 (21.1), 21.2 (20.6), 20.3 (20.0), 18.1 (17.9), 15.6 (15.1), 11.4 (11.0), 10.9. HRMS Calcd. for $C_{33}H_{52}O_6S$ 576.3485, found 576.3489.

2.22. Methyl 3α,7α-diacetyl-11β-(3-methyl)-butylsulfanyl-12α-oxo-5β,17β-cholan-24-one (8i)

Yield 205 mg (72%). Oil. IR (neat) 3353, 1718, 1374, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.27 (d, J = 4.0 Hz, 1H, H-12), 3.86 (m, 1H, H-3β), 3.31 (m, 1H, H-7β), 3.02 (dd, J = 3.6, 3.9 Hz, 1H, H-11), 2.64 (m, 2H, CH_2S), 2.04 (s, 3H, CH_3C=O), 2.01 (s, 3H, CH_3C=O), 1.13 (d, J = 6.3 Hz, 6H, $(CH_3)_2CH$), 1.06 (d, J = 6.4 Hz, 3H, H-21), 0.85 (s, 3H, H-19), 0.69 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 170.7, 170.3, 89.9, 76.1, 73.8, 49.9, 49.7, 47.2, 45.6, 44.3, 43.6, 38.2, 37.3, 35.1, 34.6, 34.0, 33.3, 32.7, 31.6, 31.0, 30.4, 28.9, 27.6, 27.3, 24.4, 23.7, 22.5, 21.6, 21.0, 20.7, 18.6, 11.1. HRMS Calcd. for $C_{33}H_{52}O_6S$ 576.3485, found 576.3491.

2.23. Methyl 3α,7α-diacetyl-11β-(1-naphthyl)sulfanyl-12α-oxo-5β,17β-cholan-24-one (8j)

Yield 200 mg (63%). Oil. IR (neat) 3387, 2951, 1734, 1471, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (m, 1H), 7.65 (m, 2H), 7.36 (m, 3H), 6.66 (m, 1H), 4.49 (d, J = 4.1 Hz, 1H, H-12), 4.33 (m, 1H, H-3β), 3.67 (m, 1H, H-7β), 3.11 (dd, J = 3.6, 3.9 Hz, 1H, H-11), 2.03 (s, 3H, CH_3C=O), 2.02 (s, 3H, CH_3C=O), 1.03 (d, J = 6.4 Hz, 3H, H-21), 0.89 (s, 3H, H-19), 0.73 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 170.9, 170.5, 135.9, 133.9, 128.9, 128.8, 128.6, 126.5, 126.4, 126.2, 124.8, 124.7, 89.4, 76.0, 73.1, 49.7, 49.5, 47.8, 44.9, 42.5, 35.3, 34.7, 33.6, 33.1, 33.0, 32.7, 31.2, 31.0, 30.6, 27.8, 27.4, 27.1, 24.0, 21.7, 21.2, 18.3, 11.3. HRMS Calcd. for $C_{38}H_{48}O_6S$ 632.3172, found 632.3178.

2.24. General procedure for the preparation of sulfones 10

0.79 mmol of compound **8** were dissolved in CH_2Cl_2 (15 mL), under argon. The solution was cooled at 0 °C and *m*-CPBA (0.39 g, 1.58 mmol) was added. After stirring at room temperature for 24 h, the mixture was hydrolyzed with a saturated solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford the corresponding sulfone **10**.

2.25. Methyl 3α,7α-diacetyl-11β-benzylsulfonyl-12α-oxo-5β,17β-cholan-24-one (10a)

Yield 375 mg (76%). Oil. IR (neat) 3387, 2951, 1719, 1359, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.16 (m, 5H), 4.82 (s, 2H, SO_2CH_2Ph), 4.54 (m, 1H, H-3β), 3.96 (d, J = 4.0 Hz, 1H, H-12), 3.57 (dd, J = 3.6, 3.9 Hz, 1H, H-11), 3.41 (m, 1H, H-7β), 2.03 (s, 3H, CH_3C=O), 2.02 (s, 3H, CH_3C=O), 1.12 (d, J = 5.6 Hz, 3H, H-21), 0.89 (s, 3H, H-19), 0.77 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$):

δ = 174.0, 170.8, 170.2, 136.3, 129.2 (2C), 127.9 (2C), 124.1, 81.4, 76.8, 74.2, 57.1, 50.6, 48.8, 44.9, 43.5, 43.1, 41.9, 40.6, 39.4, 35.7, 35.1, 34.6, 34.2, 33.8, 33.1, 31.9, 31.6, 31.0, 27.3, 21.6, 21.3, 18.7, 11.4. HRMS Calcd. for $C_{35}H_{48}O_8$ S 628.307, found 628.3075.

2.26. Methyl 3α,7α-diacetyl-11β-(p-methoxybenzyl)sulfonyl-12α-oxo-5β,17β-cholan-24-one (10b)

Yield 385 mg (74%). Oil. IR (neat) 3418, 2961, 1720, 1340, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.09 (d, J = 8.1 Hz, 2H), 6.78 (d, J = 7.9 Hz, 2H), 4.41 (m, 1H, H-3β), 4.69 (s, 2H, SO_2CH_2Ph), 3.88 (d, J = 4.1 Hz, 1H, H-12), 3.76 (s, 3H, OCH_3), 3.64 (dd, J = 3.5, 4.0 Hz, 1H, H-11), 3.46 (m, 1H, H-7β), 2.01 (s, 3H, CH_3C═O), 2.00 (s, 3H, CH_3C═O), 1.12 (s, 3H, H-19), 1.02 (d, J = 6.1 Hz, 3H, H-21), 0.77 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8, 170.6, 170.1, 159.7, 130.6 (2C), 116.9, 114.7 (2C), 82.3, 76.9, 73.7, 56.9, 56.1, 50.7, 47.9, 44.7, 44.2, 42.3, 40.7, 37.3, 36.5, 35.3, 34.1, 33.9, 33.6, 32.9, 32.4, 31.7, 29.6, 28.4, 27.6, 21.8, 21.6, 17.9, 11.5. HRMS Calcd. for $C_{36}H_{50}O_9S$ 658.3176, found 658.3180.

2.27. Methyl 3α,7α-diacetyl-11β-benzenesulfonyl-12α-oxo-5β,17β-cholan-24-one (10c)

Yield 400 mg (82%). Oil. IR (neat) 3424, 1718, 1338, 1130 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.98 (m, 2H), 7.67 (m, 2H), 7.34 (m, 1H), 4.48 (m, 1H, H-3β), 3.92 (d, J = 4.0 Hz, 1H, H-12), 3.72 (dd, J = 3.7, 3.9 Hz, 1H, H-11), 3.66 (m, 1H, H-7β), 2.04 (s, 3H, CH_3C═O), 2.00 (s, 3H, CH_3C═O), 1.06 (d, J = 6.4 Hz, 3H, H-21), 0.92 (s, 3H, H-19), 0.74 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 170.6, 169.9, 138.9, 134.2, 129.9 (2C), 127.4 (2C), 88.6, 76.4, 72.9, 50.7, 49.8, 44.8, 44.0, 42.6, 36.9, 35.7, 34.9, 34.1, 33.6, 32.9, 31.4, 31.1, 30.4, 28.4, 27.6, 24.4, 23.5, 21.6, 21.1, 17.6, 10.7. HRMS Calcd. for $C_{34}H_{46}O_8S$ 614.2913, found 614.2919.

2.28. Methyl 3α,7α-diacetyl-11β-(4-methylbenzene)sulfonyl-12α-oxo-5β,17β-cholan-24-one (10d)

Yield 390 mg (78%). Oil. IR (neat) 3353, 1715, 1345, 1128 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 4.37 (m, 1H, H-3β), 4.02 (d, J = 3.9 Hz, 1H, H-12), 3.85 (dd, J = 3.8, 4.1 Hz, 1H, H-11), 3.52 (m, 1H, H-7β), 2.39 (s, 3H, CH_3Ph), 2.03 (s, 3H, CH_3C═O), 2.02 (s, 3H, CH_3C═O), 1.13 (d, J = 6.3 Hz, 3H, H-21), 0.89 (s, 3H, H-19), 0.72 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.7, 170.8, 170.3, 141.9, 135.4, 129.6 (2C), 128.9 (2C), 83.2, 76.1, 73.9, 51.2, 50.6, 44.7, 41.2, 40.6, 36.0, 34.6, 34.0, 33.7, 33.2, 32.9, 31.0, 29.9, 29.6, 28.4, 27.6, 27.4, 24.6, 24.3, 21.7, 20.9, 17.4, 11.0. HRMS Calcd. for $C_{35}H_{48}O_8S$ 628.307 found 628.3074.

2.29. Methyl 3α,7α-diacetyl-11β-(4-methoxybenzene)sulfonyl-12α-oxo-5β,17β-cholan-24-one (10e)

Yield 365 mg (72%). Oil. IR (neat) 3455, 2965, 1718, 1374, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 4.43 (m, 1H, H-3β), 3.96 (d, J = 3.9 Hz, 1H, H-12), 3.81 (dd, J = 3.8, 4.0 Hz, 1H, H-11), 3.77 (s, 3H, OCH_3), 3.59 (m, 1H, H-7β), 2.02 (s, 3H, CH_3C═O), 2.00 (s, 3H, CH_3C═O), 1.06 (d, J = 6.4 Hz, 3H, H-21), 0.82 (s, 3H, H-19), 0.69 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 170.8, 170.1, 159.9, 131.7, 129.8 (2C), 115.1 (2C), 82.7, 76.5, 73.6, 56.4, 50.3, 49.9, 44.7, 39.4, 37.2, 36.1, 35.7, 34.4, 34.2, 33.8, 33.7, 32.6, 31.5, 31.0, 29.4, 28.3, 27.4, 26.9, 21.5, 21.1, 17.9, 11.1. HRMS Calcd. for $C_{35}H_{48}O_9S$ 644.3019, found 644.3023.

2.30. Methyl 3α,7α-diacetyl-11β-(4-fluorobenzene)sulfonyl-12α-oxo-5β,17β-cholan-24-one (10f)

Yield 375 mg (75%). Oil. IR (neat) 3429, 1726, 1330, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.01 (m, 2H), 7.32 (m, 2H), 4.03 (m, 1H, H-3β), 3.89 (d, J = 4.0 Hz, 1H, H-12), 3.71 (dd, J = 3.6, 3.9 Hz, 1H, H-11), 3.46 (m, 1H, H-7β), 2.03 (s, 3H, CH_3C═O), 2.01 (s, 3H, CH_3C═O), 1.01 (d, J = 6.3 Hz, 3H, H-21), 0.79 (s, 3H, H-19), 0.66 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 170.6, 170.2, 163.2 ($J_{C,F}$ = 261.8 Hz), 134.5, 129.9 (2C, $J_{C,F}$ = 6.4 Hz), 116.3 (2C, $J_{C,F}$ = 16.1 Hz), 83.9, 75.8, 73.3, 50.9, 50.0, 45.1, 41.7, 40.1, 36.8, 36.7, 35.3, 34.3, 34.2, 33.8, 33.4, 32.9, 32.6, 30.5, 28.4, 27.6, 27.2, 21.6, 21.3, 17.4, 10.9. HRMS Calcd. for $C_{34}H_{45}FO_8S$ 632.2819, found 632.2824.

2.31. Methyl 3α,7α-diacetyl-11β-propylsulfonyl-12α-oxo-5β,17β-cholan-24-one (10g)

Yield 180 mg (86%). Oil. IR (neat) 3422, 1724, 1335, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.96 (d, J = 4.1 Hz, 1H, H-12), 3.88 (m, 1H, H-3β), 3.64 (dd, J = 3.6, 3.9 Hz, 1H, H-11), 3.39 (m, 1H, H-7β), 3.21 (m, 2H, CH_2SO_2), 2.03 (s, 3H, CH_3C═O), 2.02 (s, 3H, CH_3C═O), 1.12 (d, J = 6.4 Hz, 3H, H-21), 0.96 (t, J = 6.5 Hz, 3H, CH_3), 0.88 (s, 3H, H-19), 0.72 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 170.2, 169.9, 82.6, 75.1, 73.3, 53.4, 51.0, 48.6, 44.7, 42.6, 41.1, 36.3, 34.4, 34.2, 33.6, 33.4, 31.6, 31.0, 30.6, 28.4, 27.6, 26.9, 25.3, 23.4, 21.9, 21.3, 17.6, 15.9, 13.6, 11.4. HRMS Calcd. for $C_{31}H_{48}O_8S$ 580.307, found 580.3075.

2.32. Methyl 3α,7α-diacetyl-11β-(2-methyl)-butylsulfonyl-12α-oxo-5β,17β-cholan-24-one (10h)

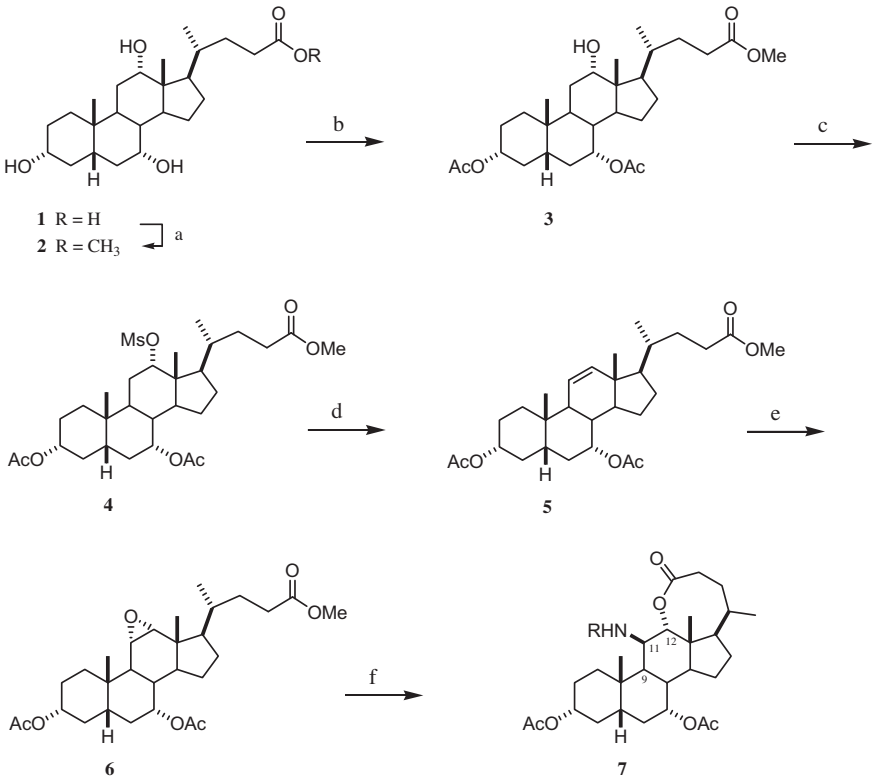
Yield 370 mg (77%). Oil. IR (neat) 3429, 1718, 1336, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.01 (d, J = 3.9 Hz, 1H, H-12), 3.87 (m, 1H, H-3β), 3.67 (dd, J = 3.6, 4.0 Hz, 1H, H-11), 3.41 (m, 1H, H-7β), 3.32 (m, 2H, CH_2SO_2), 2.03 (s, 3H, CH_3C═O), 2.01 (s, 3H, CH_3C═O), 1.19 (d, J = 6.3 Hz, 3H, CH_3CH), 1.03 (d, J = 6.4 Hz, 3H, H-21), 0.99 (t, J = 6.4 Hz, 3H, CH_3CH_2), 0.82 (s, 3H, H-19), 0.69 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 170.8, 170.3, 82.4, 74.9, 73.7, 54.7, 50.6, 48.6, 45.4, 41.2, 40.1, 37.3, 35.7, 34.9, 34.2, 33.6, 32.9, 31.0, 29.7, 29.4, 28.4, 27.6, 27.2, 26.1, 24.3, 21.6, 21.5, 19.7, 19.6, 17.9, 12.7, 11.6. HRMS Calcd. for $C_{33}H_{52}O_8S$ 608.3383, found 608.3387.

2.33. Methyl 3α,7α-diacetyl-11β-(3-methyl)-butylsulfonyl-12α-oxo-5β,17β-cholan-24-one (10i)

Yield 395 mg (82%). Oil. IR (neat) 3426, 1721, 1340, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.95 (d, J = 4.1 Hz, 1H, H-12), 3.77 (m, 1H, H-3β), 3.62 (dd, J = 3.7, 3.9 Hz, 1H, H-11), 3.54 (m, 2H, CH_2SO_2), 3.39 (m, 1H, H-7β), 2.04 (s, 3H, CH_3C═O), 2.02 (s, 3H, CH_3C═O), 1.09 (d, J = 6.4 Hz, 6H, $(CH_3)_2CH$), 1.01 (d, J = 6.3 Hz, 3H, H-21), 0.84 (s, 3H, H-19), 0.66 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 170.4, 170.1, 82.9, 75.8, 73.1, 50.8, 48.9, 48.0, 45.3, 44.7, 39.6, 37.3, 35.7, 34.2, 33.9, 33.2, 32.8, 32.4, 31.7, 31.3, 29.4, 28.7, 27.4, 27.1, 26.9, 23.6, 23.1, 21.8, 21.3, 20.6, 18.4, 11.1. HRMS Calcd. for $C_{33}H_{52}O_8S$ 608.3383, found 608.3386.

2.34. Methyl 3α,7α-diacetyl-11β-naphthylsulfonyl-12α-oxo-5β,17β-cholan-24-one (10j)

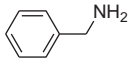
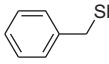
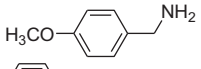
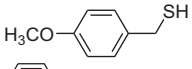
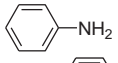
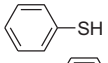
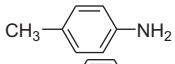
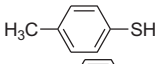
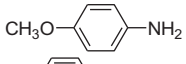
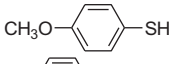
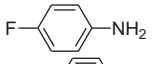
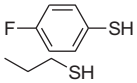
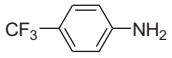
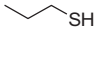
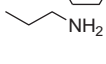
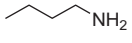
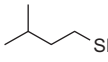
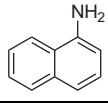
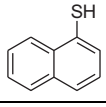
Yield 355 mg (68%). Oil. IR (neat) 3436, 1715, 1356, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.36 (m, 1H), 8.04 (m, 2H), 7.87 (m, 3H), 7.41 (m, 1H), 4.09 (d, J = 4.1 Hz, 1H, H-12), 4.29 (m, 1H, H-3β), 3.73 (dd, J = 3.8, 4.0 Hz, 1H, H-11), 3.56 (m, 1H, H-7β), 2.03 (s, 3H, CH_3C═O), 2.02 (s, 3H, CH_3C═O), 1.07 (d, J = 6.4 Hz, 3H, H-21), 0.83



Reaction conditions : (a) MeOH, PTSA, Δ, 99%; (b) Ac_2O, pyridine, DMAP, 87%; (c) MsCl, pyridine, 0° C to r.t., 24 h, 100%; (d) AcOK, HMPT, 100 °C, 48 h, 80%; (e) *m*-CPBA, CH_2Cl_2, r.t., 24 h, 92%; (f) RNH_2, EtOH/toluene (1/1), Δ, 24 h.

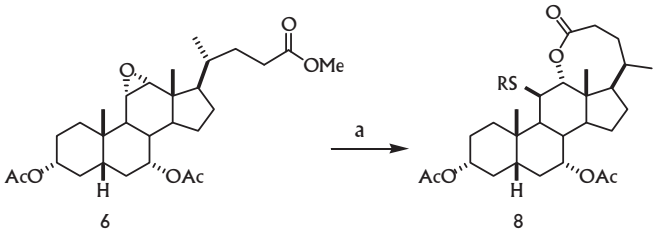
Scheme 2. Stereoselective synthesis of 11-amino-cholano-24,12-lactones from cholic acid.

Table 1
Pentacyclic steroids **7a-j** and **8a-j**.

Entry	Amines RNH_2	Yield[a] of **7**	Thiols RSH	Yield[a] of **8**
1		**7a**: 81%		**8a**: 72%
2		**7b**: 65%		**8b**: 62%
3		**7c**: 88%		**8c**: 82%
4		**7d**: 67%		**8d**: 64%
5		**7e**: 64%		**8e**: 65%
6		**7f**: 83%		**8f**: 78%
7		**7g**: 72%		**8g**: 66%
8		**7h**: 70%		**8h**: 62%
9		**7i**: 75%		**8i**: 72%
10		**7j**: 66%		**8j**: 63%

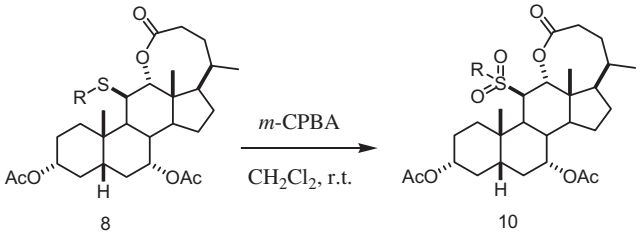
[a] Yields are given for isolated products.

(s, 3H, H-19), 0.69 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 170.7, 170.3, 139.4, 138.7, 134.9, 129.6, 128.4, 127.8, 126.9, 126.7, 126.0, 124.9, 82.6, 75.1, 73.6, 51.2, 50.6, 49.8, 45.9, 39.4, 36.9, 35.6, 34.2, 33.9, 33.7, 32.8, 32.1, 31.7, 31.5, 28.9, 27.6,



Reaction condition : (a) RSH, EtOH/toluene (1/1), 24 h.

Scheme 3. Stereoselective synthesis of 11-thio-cholano-24,12-lactones from cholic acid.



Scheme 5. Synthesis of sulfones **10**.

27.2, 22.1, 21.9, 21.4, 17.6, 10.9. HRMS Calcd. for $C_{38}H_{48}O_8S$ 664.307, found 664.3076.

2.35. Methyl 3α,7α-diacetyl-11β-cyanylseleno-12α-oxo-5β,17β-cholan-24-one (11)

Epoxide [6] (0.5 g, 1 mmol) and potassium selenocyanate (0.15 g, 1 mmol) in acetone (30 mL) were heated under reflux for 24 h. After evaporation of the solvent, the product was dissolved in diethyl ether (20 mL). The solution was washed with saturated brine (10 mL) and with water (10 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent left a residue, which was chromatographed on silica gel, eluted with petroleum ether/diethyl ether: 7/3. Compound **11** was isolated in 66% yield (0.38 g) as an oil.

IR (neat) 3349, 2931, 2128, 1352, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.37 (m, 1H, H-3β), 3.98 (d, J = 4.0 Hz, 1H, H-12), 2.52 (dd, J = 3.6, 3.9 Hz, 1H, H-11), 3.51 (m, 1H, H-7β), 2.03 (s, 3H, CH_3C═O), 2.02 (s, 3H, CH_3C═O), 1.09 (d, J = 5.6 Hz, 3H, H-21), 0.88 (s, 3H, H-19), 0.72 (s, 3H, H-18); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 170.5, 170.1, 101.8, 78.7, 75.3, 70.8, 50.3, 48.6, 44.2, 39.4, 37.8, 36.4, 35.3, 34.9, 33.8, 33.2, 32.6, 31.2, 30.6, 29.3, 28.4, 27.6, 27.1, 24.6, 21.9, 21.6, 18.3, 10.9. HRMS Calcd. for $C_{29}H_{41}NO_6Se$ 579.2099, found 579.2103.

3. Results and discussion

We recently described a new synthesis of pentacyclic steroids by stereoselective epoxide ring opening [18] (Scheme 2). Our strategy is based on a diastereoselective epoxidation and a stereoselective epoxide ring opening employing nucleophilic species. The methyl 3,7-diacetylchol-11-enate **5** was prepared from cholic acid, a commercial bile acid inexpensive and readily available, according to the previously described procedure [15] in 4 steps and a 70% overall yield. Epoxidation of **5** with *m*-CPBA in CH_2Cl_2 afforded the 11α,12α-epoxide **6** in high selectivity and good yield. Then, a selective epoxide ring opening was applied with nucleophilic amines. During this step, an intramolecular lactonization was also observed leading to the corresponding 11-amino-cholano-24,12-lactones **7**. This reaction, stereo- and regioselective, was very efficient. The yields of the relative lactones were depicted in Table 1.

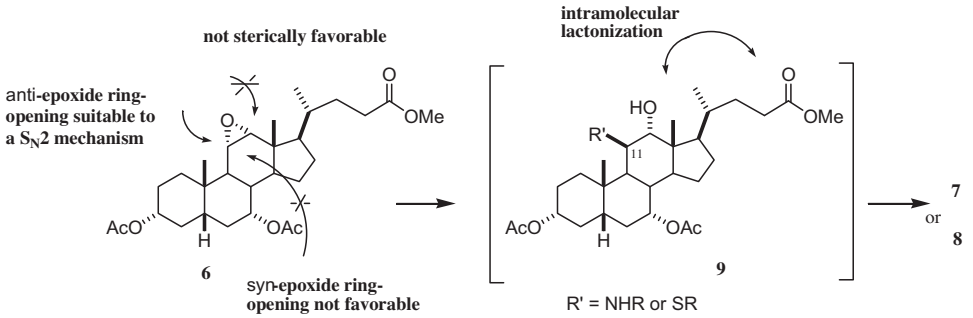
Table 2
Sulfones **10a-j**.

Entry **8**	Product **10**: yield
8a	76%
8b	74%
8c	82%
8d	78%
8e	72%
8f	75%
8g	86%
8h	77%
8i	82%
8j	68%

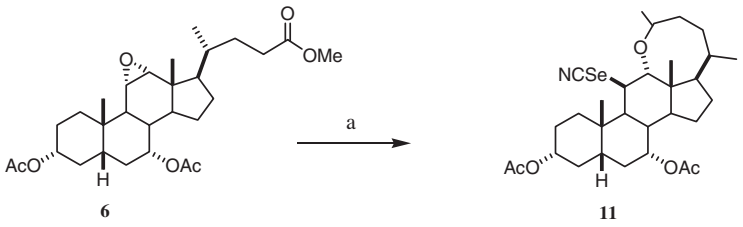
As a continuation of our synthetic and stereochemical studies on steroidal systems containing an heteroatom, a similar strategy was used to obtain pentacyclic steroids **8** possessing a thiol function at the C-11 position (Scheme 3). Thus, 11α,12α-epoxide **6** was treated with different nucleophilic thiols in EtOH/toluene (1/1) at reflux during 24 h, affording steroidal lactones **8**. The yields of these new lactones are depicted in Table 1. Here too, the reaction was very efficient, stereo- and regioselective, and this selectivity can be rationalized as shown in Scheme 4. The structure of these new pentacyclic steroids **8** was completely characterized by NMR (400 MHz) and mass spectroscopic methods (see experimental part). The NMR spectra showed a disappearance of the characteristic singlet of the lateral chain at δ_H 3.6 ppm (s, C-24-OMe) and the signal of H-(11) ($J \sim 4$ Hz) confirm its α position.

As depicted in Scheme 4, the nucleophilic attack in the α-epoxide ring opening, made exclusively on the least sterically hindered carbon epoxide (C11) (S_N2 mechanism), produces a *trans*-hydroxy amine or sulfide **9**, which is not isolated.

It is worth pointing out, by analyzing Table 1, that the epoxide ring opening is not sensitive to electronic effects of the aromatic moiety in



Scheme 4. Proposed mechanism of epoxide ring opening.



6 11

Reaction condition : (a) KSeCN, acetone, Δ, 24 h, 66%.

Scheme 6. Stereoselective synthesis of a steroidal 11-selenocyanate **11**.

the amines or thiols. Good yields were obtained with nucleophiles possessing both activating and deactivating R groups. The reaction is also not sensitive to steric effects as shown by the entry 10: the bulky naphthyl group was introduced in good yield (Table 1).

We turned then our attention to the preparation of steroidal sulfone derivatives. The synthetic utility of organic sulfur compounds has been reviewed [19–22]. Otherwise, compounds containing a sulfide, sulfoxide or sulfone moiety present not only a synthetic interest but also for some of them a medicinal relevance [23,24]. Indeed, during metabolism organic sulfides can undergo oxidation to sulfoxides and then to sulfones [25]. Thus, for example, tazofelone an inflammatory bowel disease agent, undergoes oxidative metabolism forming stereoisomeric sulfoxides [26].

So, we envisaged to oxidize our 11-thio-cholano-24,12-lactones by using a chemical method [27,28]. The reaction was conducted with 2 equiv of *m*-CPBA in dichloromethane at room temperature (Scheme 5). The corresponding steroids **10a-j** possessing a sulfone moiety at C-11, were isolated in good yields as reported in Table 2.

Having transformed efficiently our 11-thio derivatives into sulfones, we turned then our attention to the introduction of a selena moiety at the C-11 position of the steroidal skeleton. Organoselenium compounds have been documented as promising pharmacological agents against a number of diseases. Indeed, compounds containing selenium can possess biological properties and have been used as antiviral, antihypertensive, antibacterial or chemopreventive anticancer agents [29,30]. There are several reports in the literature describing the antitumoral activity of selenium compounds *via* apoptosis in cancer cells induced by the generation of ROS in a pro-oxidant fashion [31–35].

Thus, epoxide **6** was dissolved in acetone containing potassium selenocyanate [36] and was heated under reflux for 24 h, to give the steroidal selenocyanate **11** in good yield (see Scheme 6).

In conclusion, this paper describes a versatile and stereoselective synthesis of pentacyclic steroids from commercially available cholic acid. Moreover, all these steroids possess a functional group at the C-11 position of the steroidal skeleton, which is a key position from a biological point of view. The key steps of this synthesis are an asymmetric epoxidation and a stereoselective epoxide ring opening. Tests to check the biological activity of these steroids and application of this strategy to obtain new structures are being conducted by our group.

Acknowledgements

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