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Synthesis of various secosteroidal macrocycles by ring-closing metathesis

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ABSTRACT

We set out to describe an efficient and versatile method for preparing secosteroidal macrocycles from cholic acid, *via* an oxidative ring-expansion/ring-opening sequence and a ring-closing metathesis reaction 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.

Secosteroids have attracted considerable interest because of the broad range of biological activities of many naturally occurring representatives, such as Vitamins D [1], anolides [2], and marine steroids [3,4]. Apart from Vitamins D with their innumerable biological effects [5], secosteroids with cytotoxic [6–8], antihistamine [9], and anticancer [10] activity should be mentioned as compounds with great potential for drug development. The activity of seco analogs of normal steroidal hormones in humans and higher animals is a matter of scientific interest as well. Some of these compounds were prepared synthetically and showed hormonal or antihormonal activity [11–16]. It is evident that the higher conformational flexibility of seco steroids in comparison with normal steroids may result in novel, pharmaceutically useful compounds.

Otherwise, macrocyclic compounds have unique physicochemical and topological properties that allow them to exhibit unusual biological properties [17,18]. Macrocycles have the ability to exhibit high target binding affinity, selectivity, and improved oral bioavailability. Additionally, macrocyclization is an efficient way of increasing cellular penetration via the decrease in polarity of peptidic drug leads [19]. Macrocycles have been proven to be efficient as protease inhibitors [20,21], G protein- coupled receptors (GPCRs) [22–24], and protein–protein interaction inhibitors [25,26]. Natural products are one of the sources of bioactive macrocycles such as erythromycin, rapamycin, vancomycin, cyclosporine, and epothilone [27]. Natural products exhibit enormous structural diversity [28]. However, there are several problems associated with their use in screening experiments including difficulties with purification, bioactive component identification, structural assignment, chemical modification, and analog synthesis [29]. These difficulties have motivated medicinal chemistry researchers to develop strategies such as diversity oriented synthesis (DOS) of macrocyclic compounds with known bioactive domains such as peptide motifs [30–32].

Consequently, many bioactive macrocycles with diversity and complexity are now readily available in chemist's showcases [33,34].

So, it would be interesting to combine secosteroidal skeleton with varied types of macrocycles in order to obtain a new class of biological molecules. We report herein an efficient synthesis of secosteroidal macrocycles from cholic acid **1** (Scheme 1). We show that we can modify the size of the macrocycle and then lead to novel interesting structures. 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. NMR signals assignments were made with the aid of a combination of 2D homonuclear (^{1}H–^{1}H) and heteronuclear (^{1}H–^{13}C) correlation

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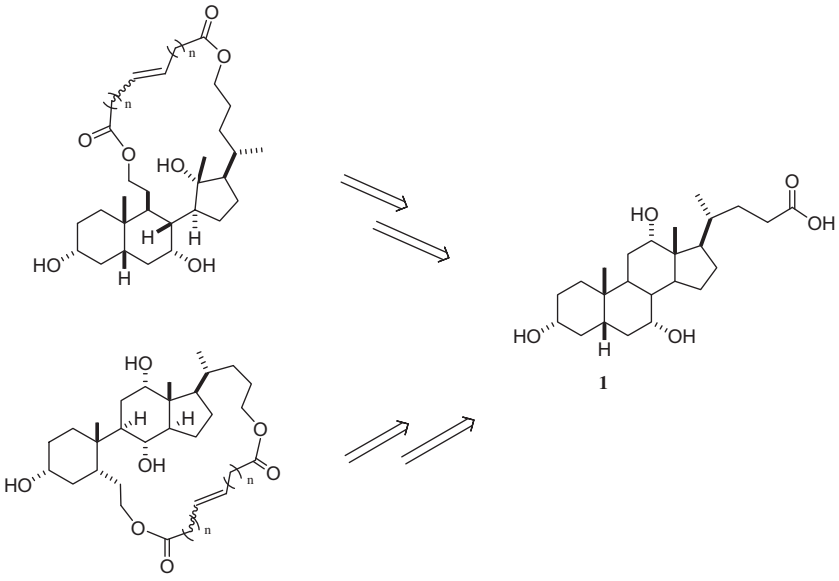


Scheme 1. Retrosynthetic pathway.

techniques, which included ^1H–^1H COSY, ^1H–^1H Nuclear Overhauser Effect Spectroscopy (NOESY), Heteronuclear Single Quantum Correlation (HSQC) and Heteronuclear Multiple Bond Correlation (HMBC). IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. Flash chromatography was performed on silica gel (Merk 60 F254) and TLC on silica gel. Dichloromethane was distilled from P2O5 and tetrahydrofuran (THF) over sodium/benzophenone.

Compounds **14** and **15** were prepared according to the previously described procedure [35]. The nomenclature used for the steroids is not the nomenclature used by Chemical Abstracts [36,37].

2.1. Methyl 3α,7α-dimethoxy-12α-hydroxy-5β-cholan-24-oate (*3*)

To a stirred suspension of NaH (0.62 g, 26 mmol) in THF (10 mL) at 0 °C under argon was added a solution of triol **2** (5 g, 11.8 mmol) in 5 mL of THF. The reaction mixture was stirred for 15 min, and then iodomethane (367 μL, 5.9 mmol) was added dropwise. After 24 h at room temperature, the reaction was diluted with 10 mL of Et_2O and quenched by the slow addition of 10 mL of H_2O. The combined organic extracts (3 × 10 mL) were washed with 30 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (Et_2O: 100%) to give **7** (5 g, 94%) as a white solid. mp = 80 °C; ^1H NMR (300 MHz, $CDCl_3$): 0.59 (s, 3H, H-18), 0.83 (d, *J* = 6.5, 3H, H-21), 0.85 (s, 3H, H-19), 2.94 (m, 1H, H-3β), 3.14 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 3.21 (m, 1H, H-7β), 3.26 (s, 3H, OCH_3), 3.29 (m, 1H, H-12β); ^{13}C NMR (75 MHz, $CDCl_3$): 12.6, 17.5, 22.1, 23.0, 23.3, 26.4, 26.6, 27.5, 27.9, 28.1, 30.9, 31.2, 34.5, 35.2, 35.6, 39.8, 42.1, 42.8, 46.3, 46.4, 55.5, 55.8, 56.0, 77.3, 81.0, 82.1, 180.3. HRMS (EI) for $C_{27}H_{46}O_5$ [M^+] calcd 450.3345 found 450.3348.

2.2. Methyl 3α,7α-dimethoxy-12-oxo-5β-cholan-24-oate (*4*)

Alcohol **3** (1 g, 2.22 mmol) was mixed in a mortar with pyridinium chlorochromate (PCC) (0.57 g, 2.66 mmol). The mixture was transferred to a pressure-resistant tube (pyrex) and irradiated with MW at 170 °C for 5 min. After cooling to room temperature, the reaction mixture was filtered through a Celite pad and the filtrate and washings (CH_2Cl_2, 3 ∗ 10 mL) were combined and evaporated under reduced pressure. The residue was chromatographed on silica gel (diethyl ether/petroleum ether: 7/3), to afford 0.66 g (70% yield) of 12-oxo steroid **4** as colorless needles. mp = 71–72 °C; IR (neat) 3236, 1736, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.85 (d, *J* = 6.5, 3H, H-21), 1.02 (s, 3H, H-18), 1.03 (s, 3H, H-19), 3.26 (m, 1H, H-3β), 3.28 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.38 (m, 1H, H-7β), 3.66 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 18.4, 21.3, 21.4, 22.0, 23.7, 26.4, 27.3, 30.3, 30.9, 31.1, 31.2, 31.3, 34.4, 35.4, 35.6, 37.8, 40.4, 46.2, 51.4, 53.0, 57.1, 57.5, 58.4, 73.4, 78.4, 174.7, 214.0. HRMS (EI) for $C_{27}H_{44}O_5$ [M^+] calcd 448.3189 found 448.3192.

2.3. 3α,7α-Dimethoxy-13-oxa-C-homo-cholan-12-one (*5*)

To a solution of ketone **4** (0.5 g, 1.11 mmol) in dry dichloromethane (30 mL) containing *p*-toluenesulfonic acid (167 mg, 1.11 mmol) *m*-chloroperbenzoic acid (12 mg) was added. The solution was stirred for 24 h at room temperature. The solution was then diluted with water and extracted with dichloromethane (3 ∗ 15 mL). The solution was washed successively with a 5% $Na_2S_2O_3$ solution (10 mL), saturated brine (10 mL), and water (20 mL) and was dried over anhydrous magnesium sulfate. The oily product, obtained by evaporation of the solvent, was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH: 95/5) to afford 0.51 g of pure lactone **5** (98%) as an oil. ^1H NMR (300 MHz, $CDCl_3$): 0.86 (s, 3H, H-19), 1.05 (d, *J* = 6.4, 3H, H-21), 1.34 (s, 3H, H-18), 3.25 (m, 1H, H-3β), 3.28 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.35 (m, 1H, H-7β); ^{13}C NMR (75 MHz, $CDCl_3$): 14.5, 15.3, 17.7, 22.3, 24.2, 25.2, 26.1, 26.5, 27.5, 31.6, 32.8, 34.6, 35.2, 35.9, 36.3, 41.2, 42.5, 50.1, 55.7, 57.4, 58.5, 73.3, 76.9, 80.2, 86.9, 174.8, 176.5. HRMS (EI) for $C_{27}H_{44}O_6$ [M^+] calcd 464.3138 found 464.3143.

2.4. 3α,7α-Dimethoxy-11,12-seco-5β-cholan-12,13α,24-triol (*6*)

A solution of methyl ester **5** (1 g, 2.15 mmol) in dry ether (10 mL) was added in one portion to a suspension of $LiAlH_4$ (0.25 g, 6.46 mmol) in dry ether (20 mL) at room temperature. After 1 h the reaction was quenched with H_2O (15 mL) and EtOAc (15 mL). The aqueous layer was acidified to pH 2 with diluted HCl, and layers were separated. The aqueous layer was further extracted with EtOAc (3 × 50 mL), and the combined organic layers

were dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH: 9/1) to afford 0.83 g of pure triol **6** (88%) as an oil. IR (neat) 3280 (OH), 1220, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.06 (d, J = 6.5, 3H, H-21), 1.16 (s, 3H, H-19), 1.50 (s, 3H, H-18), 2.78 (m, 1H, H-3β), 2.79 (m, 1H, H-7β), 3.24 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 3.37 (m, 2H, H-24), 3.53 (m, 2H, H-12β); ^{13}C NMR (75 MHz, $CDCl_3$): 19.1, 19.5, 19.7, 23.5, 24.4, 24.6, 29.9, 30.8, 31.6, 32.0, 33.8, 34.1, 35.7, 38.4, 40.8, 46.2, 46.3, 51.0, 57.1, 57.4, 59.3, 61.6, 74.9, 82.4, 82.9, 89.2. HRMS (EI) for $C_{26}H_{48}O_5$ [M^+] calcd 440.3502 found 440.35.09.

2.5. 3α,7α-Dimethoxy-12,24-diallyloxy-11,12-seco-5β-cholan-13α-ol (**7**)

To a stirred suspension of KH (0.32 g, 6.81 mmol) in DMF (10 mL) at 0 °C under argon was added a solution of triol **6** (1 g, 2.27 mmol) in 5 mL of DMF. The reaction mixture was stirred for 15 min, and then allyl bromide (6.43 mL, 4.99 mmol) was added dropwise. After 48 h at room temperature, the reaction was diluted with 10 mL of Et_2O and quenched by the slow addition of 10 mL of H_2O. The solution was extracted with diethyl ether (3 ∗ 10 mL) and the combined organic extracts were washed with 30 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (Et_2O: 100%) to give **7** (0.68 g, 58%) as an oil. IR (neat) 2951, 1175, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.05 (d, J = 6.4, 3H, H-21), 1.16 (s, 3H, H-19), 1.43 (s, 3H, H-18), 2.79 (m, 1H, H-3β), 2.82 (m, 1H, H-7β), 3.24 (s, 3H, OCH_3), 3.32 (m, 2H, H-24), 3.25 (s, 3H, OCH_3), 3.38 (m, 1H, H-12β), 4.16 (m, 2H, OCH_2–CH═), 4.48 (m, 2H, OCH_2–CH═), 5.23 (m, 4H, CH_2═), 5.78 (m, 2H, CH═); ^{13}C NMR (75 MHz, $CDCl_3$): 17.9, 18.8, 24.2, 24.9, 26.1, 26.4, 28.1, 28.2, 29.3, 29.9, 31.9, 32.1, 32.1, 32.8, 33.2, 33.8, 35.7, 41.1, 45.6, 51.2, 57.0, 57.1, 71.2, 72.8, 74.5, 74.9, 82.2, 82.9, 116.3, 116.7, 131.9, 132.8. HRMS (EI) for $C_{32}H_{56}O_5$ [M^+] calcd 520.4128 found 520.4133.

2.6. General procedure for ring-closing metathesis reaction

A solution of the secosteroidal ester **7** in dry toluene (c = 0.15–0.20 mM) was stirred for 5 min in 80 °C and then Grubbs II catalyst (5 mol%) was added to the mixture. Reaction was stirred for 15 min under 80 °C and its progress was monitored by TLC. The total amount of catalyst (20 mol%) was added portionwise to the reaction mixture with stirring within 12 of 24 h. After cooling to room temperature, the reaction was quenched with ethyl vinyl ether and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (CH_2Cl_2/MeOH: 9/1), to give macrocycle **8** as an oil.

The above method was also used for the RCM reactions of secosteroids **10a-b**, **19** and **22a-b**.

2.7. Macrocycle (**8**)

Yield 50 mg (65%). Oil. IR (neat) 2981, 1370, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 1.04 (d, J = 6.4, 3H, H-21), 1.18 (s, 3H, H-19), 1.38 (s, 3H, H-18), 2.79 (m, 1H, H-3β), 2.80 (m, 1H, H-7β), 3.24 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 3.62 (m, 4H, H-24 and H-12), 4.16 (m, 4H, OCH_2–CH═), 5.92 (td, 1H, J = 6.4 and 15.2, CH═), 6.04 (td, 1H, J = 6.4 and 15.2, CH═); ^{13}C NMR (75 MHz, $CDCl_3$): 18.2, 18.7, 19.4, 23.8, 24.6, 24.9, 25.0, 25.4, 25.7, 29.8, 29.9, 32.8, 35.7, 35.9, 36.4, 37.8, 42.0, 45.6, 56.8, 57.1, 60.6, 70.8, 71.1, 71.4, 73.6, 74.2, 82.5, 82.7, 122.1, 126.8. HRMS (EI) for $C_{30}H_{52}O_5$ [M^+] calcd 492.3815 found 492.3821.

2.8. General procedure for deprotection with trimethylsilyl iodide

To a solution of macrocycle **8** (50 mg, 0.10 mmol) in chloroform (20 mL) was added trimethylsilyl iodide (0.1 mL). The solution was left overnight at room temperature. Methanol (5 mL) was then added to decompose any excess trimethylsilyl iodide. The solution was extracted with diethyl ether (3 × 10 mL), washed with water (10 mL) and saturated brine (10 mL), dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude product, which was purified by chromatography on silica gel (CH_2Cl_2/MeOH: 95/5), to give triol **9**.

The above method was also used for deprotection of macrocycles **13a-b**.

2.9. Macrocycle (**9**)

Yield 47 mg (92%). Oil. IR (neat) 3429, 2950, 1606, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 0.88 (d, J = 6.4 Hz, 3H, H-21), 0.89 (s, 3H, H-19), 1.12 (s, 3H, H-18), 3.38 (m, 2H, H-12β and H-24), 3.66 (m, 1H, H-7), 3.88 (m, 1H, H-3β), 4.16 (m, 4H, OCH_2–CH═), 5.82 (td, J = 6.3 and 15.6 Hz, 1H, CH═), 5.98 (td, J = 6.2 Hz and 15.6 Hz, 1H, CH═); ^{13}C NMR (75 MHz, $CDCl_3$): 18.8, 19.7, 23.3, 23.4, 24.2, 25.6, 29.5, 29.9, 31.5, 32.2, 33.1, 35.7, 36.4, 38.2, 41.4, 45.6, 50.8, 53.8, 59.0, 63.4, 67.2, 69.0, 70.6, 71.7, 72.2, 74.6, 119.4, 125.8. HRMS (EI) for $C_{28}H_{48}O_5$ [M^+] calcd 464.3502 found 464.3507.

We give the characterization data for compounds **10-15** later in the Experimental Section.

2.10. Methyl 3α,12α-dihydroxy-7-oxo-8-oxa-B-homo-cholan-24-oate (**16**)

To a solution of ketone **15** (3 g, 7.14 mmol) in dry dichloromethane (30 mL) containing *p*-toluenesulfonic acid (1.11 g, 6.43 mmol) *m*-chloroperbenzoic acid (1.84 g, 10.7 mmol) was added. The solution was stirred for 24 h at room temperature. The solution was then diluted with water (20 mL) and extracted with dichloromethane (3 ∗ 15 mL). The solution was washed successively with a 5% $Na_2S_2O_3$ solution, saturated brine, and water and was dried over anhydrous magnesium sulfate. The oily product, obtained by evaporation of the solvent, was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH: 95/5) to afford 2.55 g of pure lactone **5** (82%) as an oil. ^1H NMR (300 MHz, $CDCl_3$): 0.66 (s, 3H, H-18), 0.89 (d, J = 6.4, 3H, H-21), 0.96 (s, 3H, H-19), 3.58 (s, 3H, OCH_3), 3.89 (m, 1H, H-3β), 4.18 (m, 1H, H-12β); ^{13}C NMR (75 MHz, $CDCl_3$): 12.5, 14.1, 17.3, 20.7, 23.1, 24.9, 27.3, 28.9, 30.8, 31.1, 34.7, 34.9, 35.8, 36.7, 41.6, 45.0, 47.1, 51.5, 53.6, 60.4, 70.4, 71.2, 80.4, 174.6, 175.1. HRMS (EI) for $C_{25}H_{40}O_6$ [M^+] calcd 436.2825 found 436.2829.

2.11. Methyl 3α,12α-di(tert-butyldimethylsilyloxy)-7-oxo-8-oxa-B-homo-cholan-24-oate (**17**)

To a solution of lactone **16** (2 g, 4.59 mmol) in dry DMF (30 mL) containing imidazole (1.40 g, 20.6 mmol) *tert*-butyldimethylsilyl chloride (3.11 g, 20.6 mmol) was added at 0 °C. The solution was stirred for 12 h at room temperature. The solution was then diluted with water (10 mL) and extracted with dichloromethane (3 ∗ 15 mL). The combined organic extracts were washed with 30 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (Et_2O: 100%) to give **17** (2.77 g, 91%) as an oil. ^1H NMR (300 MHz, $CDCl_3$): 0.59 (12H, s, $Si(CH_3)_2$), 0.77 (9H, s, $C(CH_3)_3$), 0.82 (9H, s, $C(CH_3)_3$), 0.89 (3H, d, J = 6.4 Hz, H-21), 0.94 (3H, s, H-19), 2.92 (1H, m, H-8β), 3.57 (3H, s, OCH_3), 3.85 (1H, m, H-3β), 4.12 (1H, m, H-12β); ^{13}C NMR (75 MHz, $CDCl_3$): −4.6 (2C),

−3.4 (2C), 12.7, 15.4, 17.5, 18.1, 18.2, 23.5, 24.6 (2C), 25.8, 26.0, 27.3, 28.7, 30.6, 30.8, 31.2, 34.8, 34.9, 35.2, 35.8, 36.1, 37.3, 42.0, 42.6, 45.5, 47.1, 47.2, 51.7, 65.9, 71.4, 71.7, 79.9, 174.5, 174.8. HRMS (EI) for $C_{37}H_{68}O_6Si_2$ [M^+] calcd 664.4554 found 664.4559.

2.12. 3α,12α-di(tert-butyldimethylsilyloxy)-7,8-seco-5β-cholan-7,8α,24-triol (**18**)

A solution of diprotected lactone **17** (2 g, 3.01 mmol) in dry ether (30 mL) was added in one portion to a suspension of $LiAlH_4$ (0.46 g, 12.0 mmol) in dry ether (20 mL) at 0 °C. After 12 h at room temperature, the reaction was quenched with H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was acidified to pH 2 with diluted HCl, and layers were separated. The aqueous layer was further extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH: 9/1) to afford 1.74 g of pure triol **18** (90%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): 0.00 (12H, s, $Si(CH_3)_2$), 0.62 (s, 3H, H-18), 0.82 (18H, s, $C(CH_3)_3$), 0.88 (3H, d, *J* = 6.4 Hz, H-21), 0.94 (3H, s, H-19), 3.50 (m, 1H, H-8β), 3.56 (m, 2H, H-24), 3.72 (m, 2H, H-12β and H-3β), 3.82 (m, 4H, H-24 and H-7); ^{13}C NMR (75 MHz, $CDCl_3$): −4.5 (2C), −3.4 (2C), 12.9, 15.3, 18.4, 19.4 (2C), 21.0, 23.9, 25.8 (2C), 26.4, 27.2, 28.9, 29.3, 30.1, 31.7, 31.8, 32.8, 33.4, 35.9, 36.1, 37.3, 37.6, 41.4, 44.3, 47.4, 47.9, 52.1, 63.2, 65.9, 72.5, 72.9, 73.6. HRMS (EI) for $C_{36}H_{72}O_5Si_2$ [M^+] calcd 640.4918 found 640.4923.

2.13. 3α,12α-di(tert-butyldimethylsilyloxy)-7,24-diallyloxy-7,8-seco-5β-cholan-8α-ol (**19**)

To a stirred suspension of KH (112 mg, 2.34 mmol) in DMF (10 mL) at 0 °C under argon was added a solution of triol **18** (0.5 g, 0.78 mmol) in 5 mL of DMF. The reaction mixture was stirred for 15 min, and then allyl bromide (152 μL, 1.72 mmol) was added dropwise. After 48 h at room temperature, the reaction was diluted with 10 mL of Et_2O and quenched by the slow addition of 10 mL of H_2O. The combined organic extracts (3 ∗ 10 mL) were washed with 30 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (Et_2O: 100%) to give **18** (315 mg, 56%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): 0.02 (12H, s, $Si(CH_3)_2$), 0.65 (s, 3H, H-18), 0.83 (18H, s, $C(CH_3)_3$), 0.89 (3H, d, *J* = 6.4 Hz, H-21), 0.94 (3H, s, H-19), 3.40 (m, 1H, H-3β), 3.46 (m, 1H, H-8β), 3.56 (m, 2H, H-24), 3.88 (m, 3H, H-12β and H-7), 4.20 (m, 2H, OCH_2–CH=), 4.62 (m, 2H, OCH_2–CH=), 5.20 (m, 4H, CH_2=), 5.87 (m, 2H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): −4.4 (2C), −3.5 (2C), 13.4, 17.9, 18.3 (2C), 24.6, 24.9, 26.1 (2C), 27.5, 29.6, 30.4, 31.0, 31.8, 31.9, 32.1, 33.5, 35.2, 36.0, 36.2, 37.4, 37.5, 38.2, 41.5, 42.6, 47.3, 47.6, 47.7, 63.5, 68.4, 70.9, 72.1, 72.7, 74.5, 79.1, 116.5, 116.8, 134.7, 134.9. HRMS (EI) for $C_{42}H_{80}O_5Si_2$ [M^+] calcd 720.5544 found 720.5549.

2.14. Macrocycle (**20**)

Yield 95 mg (90%). Oil. IR (neat) 3455, 2976, 1606 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (major isomer): 0.00 (12H, s, $Si(CH_3)_2$), 0.64 (s, 3H, H-18), 0.83 (18H, s, $C(CH_3)_3$), 0.83 (3H, s, H-19), 0.88 (3H, d, *J* = 6.4 Hz, H-21), 3.57 (m, 1H, H-8β), 3.72 (m, 1H, H-3β), 3.90 (m, 1H, H-12β), 4.36 (m, 4H, OCH_2–CH=), 4.88 (m, 4H, H-24 and H-7), 6.12 (td, *J* = 6.4 Hz, *J* = 15.3 Hz, 1H, CH=), 6.17 (td, *J* = 6.2 Hz, *J* = 15.3 Hz, 1H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): −4.4 (2C), −3.6 (2C), 12.7, 13.1, 15.4, 17.9, 18.3 (2C), 24.6, 24.7 (2C), 25.3, 26.0, 27.6, 28.3, 29.7, 30.4, 31.5, 31.9, 32.4, 33.0, 35.2, 36.0, 36.2, 37.5, 41.9, 44.6, 47.2, 47.6, 63.7, 66.0, 71.2, 72.3, 72.2, 72.3, 72.7, 129.2, 142.9. HRMS (EI) for $C_{40}H_{76}O_5Si_2$ [M^+] calcd 692.5231 found 692.5235.

2.15. General procedure for deprotection with TBAF

To a solution of macrocycle **20** (100 mg, 0.14 mmol) in anhydrous THF (20 mL) was added tetra-*n*-butylammonium fluoride (0.35 mL, 1 M, 2.4 equiv). The solution was left overnight at room temperature. The solution was extracted with diethyl ether, washed with water and saturated brine, dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude product, which was purified by chromatography on silica gel (CH_2Cl_2/MeOH: 9/1), to give triol **21** (60 mg, 92%) as an oil.

The above method was also used for deprotection of macrocycles **24a-b**.

2.16. Macrocycle **21**

IR (neat) 2965, 1340, 1059 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (major isomer): 0.66 (s, 3H, H-18), 0.86 (d, *J* = 6.4 Hz, 3H, H-21), 0.88 (s, 3H, H-19), 3.52 (m, 1H, H-8β), 3.66 (m, 1H, H-3β), 3.88 (m, 1H, H-12β), 4.28 (m, 4H, OCH_2–CH=), 4.82 (m, 4H, H-7 and H-24), 5.95 (td, *J* = 6.3 and 15.4 Hz, 1H, CH=), 6.12 (td, *J* = 6.3 Hz and 15.4 Hz, 1H, CH=);^{13}C NMR (75 MHz, $CDCl_3$): 13.8, 18.1, 23.7, 24.2, 24.6, 25.7, 29.5, 29.9, 31.9, 35.4, 35.7, 36.0, 36.1, 37.3, 41.4, 47.5, 51.2, 53.8, 59.0, 63.4, 67.2, 68.0, 71.7, 71.9, 72.9, 74.0, 119.8, 126.4. HRMS (EI) for $C_{28}H_{48}O_5$ [M^+] calcd 464.3502 found 464.3507.

2.17. General procedure for esterification

A solution of diprotected pentahydroxysecocholane **6** or **18** (0.78 mmol), 3-butenoic acid (0.14 g, 1.63 mmol), *N*,*N*-dicyclohexylcarbodiimide (0.14 g, 0.70 mmol) and 4-dimethyl-aminopyridine (86 mg, 0.70 mmol) in dichloromethane (5 mL) was stirred at room temperature until the reaction was completed (about 12 h). The *N*,*N*-dicyclohexyl urea was filtered off and the filtrate was washed with water, 5% acetic acid solution and again water, dried over magnesium sulfate and the solvent was evaporated to afford 3-butenoate **10a** or **22a**.

The above method was also used for preparation of esters **10b-c** from **6** and **22b-c** from **18**.

2.18. Secosteroid **10a**

Yield 350 mg (78%). Oil. IR (neat) 3280, 1220, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 0.96 (s, 3H, H-18), 1.02 (d, *J* = 6.4 Hz, 3H, H-21), 1.06 (s, 3H, H-19), 2.88 (m, 1H, H-7β), 2.92 (m, 1H, H-3β), 2.96 (m, 4H, CH_2–C=O), 3.22 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 4.16 (m, 4H, H-12 and H-24), 5.22 (m, 4H, CH_2=), 6.01 (m, 2H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): 18.6, 20.8, 23.3, 24.3, 24.7, 26.8, 31.9, 32.2, 32.5, 32.8, 33.6, 35.6, 35.7, 37.9, 38.4, 41.0, 41.2, 45.3, 47.5, 51.4, 57.2, 57.6, 64.2, 64.6, 72.5, 75.4, 81.9, 82.6, 116.9, 117.6, 128.6, 129.1, 168.4, 169.0. HRMS (EI) for $C_{34}H_{56}O_7$ [M^+] calcd 576.4026 found 576.4031.

2.19. Secosteroid **10b**

Yield 360 mg (76%). Oil. IR (neat) 3418, 2961, 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 0.98 (d, *J* = 6.4 Hz, 3H, H-21), 1.02 (s, 3H, H-18), 1.07 (s, 3H, H-19), 2.28 (m, 4H, CH_2–C=O), 2.34 (m, 4H, CH_2–C=), 2.81 (m, 1H, H-7β), 2.88 (m, 1H, H-3β), 3.23 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 4.13 (m, 4H, H-12 and H-24), 5.17 (m, 4H, CH_2=), 5.98 (m, 2H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): 18.9, 20.3, 23.7, 23.9, 24.4, 28.8, 31.1, 32.6, 32.7, 33.2, 34.0, 34.3, 34.7, 35.5, 35.9, 37.6, 38.1, 41.2, 41.7, 44.9, 47.2, 51.3, 57.2 , 57.4, 64.8,

65.1, 72.3, 75.7, 81.8, 82.3, 117.4, 118.1, 129.6, 129.9, 172.1, 172.9. HRMS (EI) for $C_{36}H_{60}O_7$ [M^+] calcd 604.4339 found 604.4344.

2.20. Secosteroid **10c**

Yield 360 mg (72%). Oil. IR (neat) 3280, 1220, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.00 (d, J = 6.4 Hz, 3H, H-21), 1.02 (s, 3H, H-18), 1.06 (s, 3H, H-19), 2.16 (m, 4H, CH_2–C═), 2.28 (m, 4H, CH_2–C═O), 2.82 (m, 1H, H-7β), 2.92 (m, 1H, H-3β), 3.23 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 4.15 (m, 4H, H-12 and H-24), 5.21 (m, 4H, CH_2═), 5.92 (m, 2H, CH═); ^{13}C NMR (75 MHz, $CDCl_3$): 18.7, 20.6, 23.3, 24.1, 24.4, 24.7, 25.6, 28.3, 31.3, 32.7, 33.0, 33.4, 34.6, 34.1, 34.9, 35.7, 36.0, 37.3, 38.4, 40.9, 41.6, 44.3, 47.8, 51.6, 57.4 , 57.7, 65.1, 65.6, 71.9, 75.3, 81.6, 82.9, 118.3, 118.7, 129.1, 129.8, 172.7, 173.0. HRMS (EI) for $C_{38}H_{64}O_7$ [M^+] calcd 632.4652 found 632.4657.

2.21. Macrocycle **11a**

Yield 60 mg (56%). Oil. IR (neat) 2951, 1732, 1370, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 0.98 (s, 3H, H-18), 1.04 (d, J = 6.4 Hz, 3H, H-21), 1.07 (s, 3H, H-19), 2.89 (m, 1H, H-7β), 2.92 (m, 4H, CH_2–C═O), 2.94 (m, 1H, H-3β), 3.23 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 4.18 (m, 4H, H-12 and H-24), 5.92 (td, J = 6.3 and 15.1 Hz, 1H, CH═), 6.09 (td, J = 6.3 Hz and 15.3 Hz, 1H, CH═); ^{13}C NMR (75 MHz, $CDCl_3$): 18.4, 20.6, 23.1, 24.6, 24.9, 27.1, 31.6, 32.4, 32.7, 33.1, 33.8, 34.9, 36.3, 37.1, 38.3, 41.6, 42.0, 45.4, 47.1, 52.3, 56.9, 57.2, 61.3, 67.2, 72.8, 75.7, 82.4, 82.9, 119.9, 126.7, 171.9, 172.6. HRMS (EI) for $C_{32}H_{52}O_7$ [M^+] calcd 548.3713 found 548.3716.

2.22. Macrocycle **11b**

Yield 55 mg (48%). Oil. IR (neat) 2965, 1728, 1609, 1502 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 1.01 (d, J = 6.4 Hz, 3H, H-21), 1.04 (s, 3H, H-18), 1.12 (s, 3H, H-19), 2.35 (m, 4H, CH_2–C═O), 2.44 (m, 4H, CH_2–C═), 2.83 (m, 1H, H-7β), 2.90 (m, 1H, H-3β), 3.24 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 4.07 (m, 4H, H-12 and H-24), 5.86 (td, J = 6.4 and 15.3 Hz, 1H, CH═), 6.01 (td, J = 6.3 Hz and 15.3 Hz, 1H, CH═); ^{13}C NMR (75 MHz, $CDCl_3$): 18.9, 21.1, 23.4, 24.9, 25.1, 27.8, 31.4, 32.1, 32.9, 33.6, 34.2, 34.9, 35.4, 36.1, 36.8, 37.4, 38.0, 42.2, 42.6, 45.9, 47.4, 52.7, 57.0, 57.7, 61.8, 68.2, 72.8, 74.9, 82.1, 82.7, 119.4, 126.1, 172.8, 173.0. HRMS (EI) for $C_{34}H_{56}O_7$ [M^+] calcd 576.4026 found 576.4031.

2.23. Secosteroid **22a**

Yield 500 mg (82%). Oil. IR (neat) 3424, 1338, 1130 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.00 (12H, s, $Si(CH_3)_2$), 0.66 (s, 3H, H-18), 0.85 (18H, s, $C(CH_3)_3$), 0.97 (3H, d, J = 6.4 Hz, H-21), 1.02 (3H, s, H-19), 3.08 (m, 1H, H-8β), 3.44 (m, 4H, CH_2–C═O), 3.55 (m, 2H, H-12 and H-3β), 3.90 (m, 4H, H-24 and H-7β), 5.18 (m, 4H, CH_2═), 5.83 (m, 2H, CH═); ^{13}C NMR (75 MHz, $CDCl_3$): −4.9 (2C), −3.6 (2C), 12.8, 17.5, 18.0, 20.9 (2C), 23.5, 25.8 (2C), 26.0, 27.6, 29.2, 30.3, 31.2, 31.5, 35.1, 37.5, 37.6, 39.0, 41.4, 41.6, 42.5, 42.9, 44.1, 46.3, 47.5, 47.8, 47.9, 49.6, 50.5, 62.2, 63.2, 72.6, 72.7, 73.4, 118.3 (2C), 130.5 (2C), 174.2, 174.4. HRMS (EI) for $C_{44}H_{80}O_7Si_2$ [M^+] calcd 776.5443 found 776.5449.

2.24. Secosteroid **22b**

Yield 470 mg (75%). Oil. IR (neat) 3280, 1356, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.00 (12H, s, $Si(CH_3)_2$), 0.64 (s, 3H, H-18), 0.83 (18H, s, $C(CH_3)_3$), 0.89 (3H, s, H-19), 0.94 (3H, d, J = 6.4 Hz, H-21), 2.40 (m, 8H, CH_2–C═O and CH_2–C═), 3.42 (m, 1H, H-8β), 3.66 (m, 1H, H-12β), 3.89 (m, 1H, H-3β), 4.08 (m, 4H, H-24 and H-7), 5.01 (m, 4H, CH_2═), 5.80 (m, 2H, CH═); ^{13}C NMR (75 MHz, $CDCl_3$): −4.8 (2C), −3.6 (2C), 12.8, 14.2, 17.5, 18.2, 20.2 (2C), 21.0, 22.7, 24.3 (2C), 25.5, 25.9, 26.3, 28.5, 28.9, 32.6, 33.9, 35.0, 35.3, 36.0, 37.2, 44.6, 47.2, 47.5, 51.6, 53.4, 53.8, 60.5, 68.3, 69.3, 72.2, 72.5, 73.8, 79.4, 115.4, 115.5, 136.3, 136.4, 1724.2, 173.4. HRMS (EI) for $C_{44}H_{84}O_7Si_2$ [M^+] calcd 804.5756 found 804.5761.

2.25. Secosteroid **22c**

Yield 480 mg (74%). Oil. IR (neat) 3429, 1330, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.00 (12H, s, $Si(CH_3)_2$), 0.65 (s, 3H, H-18), 0.83 (18H, s, $C(CH_3)_3$), 0.88 (3H, s, H-19), 0.93 (3H, d, J = 6.4 Hz, H-21), 2.04 (4H, m, CH_2–C═), 2.27 (m, 4H, CH_2–C═O), 3.53 (m, 1H, H-8β), 3.77 (m, 1H, H-12β), 3.87 (m, 1H, H-3β), 4.03 (m, 4H, H-24 and H-7), 5.01 (m, 4H, CH_2═), 5.74 (m, 2H, CH═); ^{13}C NMR (75 MHz, $CDCl_3$): −4.5 (2C), −3.6 (2C), 12.9, 17.7, 18.2 (2C), 24.2, 24.5 (2C), 24.6, 25.4, 25.9, 27.2, 27.7, 29.5, 29.7, 30.3, 31.4, 31.8, 33.1, 33.7, 34.0, 34.4, 35.0, 35.9, 36.1, 37.4, 37.5, 38.4, 39.2, 41.7, 42.4, 42.9, 44.8, 47.5, 47.7, 64.8, 64.9, 70.3, 72.2, 72.6, 115.3, 115.4, 137.8, 173.7, 173.8. HRMS (EI) for $C_{48}H_{88}O_7Si_2$ [M^+] calcd 832.6069 found 832.6074.

2.26. General procedure for the reduction of **11a-b** and **23a-b**

A flask equipped with a magnetic stirring bar, an argon outlet and a condenser was charged with NaBH4 (90 mg, 0.40 mmol) and anhydr. THF (7 mL) – diglyme (3 mL) under argon. The solution was cooled at 0 °C and then a solution composed of boron trifluoride etherate (0.42 g, 3 mmol), macrocycle **11a-b** or **23a-b** (0.18 mmol) and anhydr. THF (5 mL) was added. After completion of the reaction (TLC), it was quenched by addition of 2 N hydrochloric acid (1 mL) and water (10 mL), the product was extracted with ether (3 × 20 mL). The extracts were dried over MgSO4, filtered and then concentrated under vacuum. The residue was chromatographed on silica gel (Et2O-petroleum ether 1:1).

2.27. Macrocycle **12a**

Yield 52 mg (56%). Oil. IR (neat) 3280, 1220, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 1.02 (s, 3H, H-18), 1.06 (d, J = 6.4 Hz, 3H, H-21), 1.14 (s, 3H, H-19), 2.26 (m, 4H, CH_2–C═), 2.87 (m, 1H, H-7β), 2.92 (m, 1H, H-3β), 3.24 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 3.42 (m, 4H, H-12 and H-24), 5.88 (td, J = 6.4 and 15.3 Hz, 1H, CH═), 6.02 (td, J = 6.3 Hz and 15.3 Hz, 1H, CH═); ^{13}C NMR (75 MHz, $CDCl_3$): 18.9, 20.4, 23.6, 24.8, 25.1, 28.4, 31.8, 32.4, 32.6, 32.9, 33.4, 34.6, 36.5, 37.3, 39.1, 41.9, 42.6, 46.2, 47.3, 52.1, 56.4, 57.5, 66.8, 67.4, 70.2, 71.1, 72.4, 75.2, 82.1, 82.6, 119.8, 126.3. HRMS (EI) for $C_{32}H_{56}O_5$ [M^+] calcd 520.4128 found 520.4133.

2.28. Macrocycle **12b**

Yield 48 mg (48%). Oil. IR (neat) 2981, 1370, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 1.01 (d, J = 6.4 Hz, 3H, H-21), 1.04 (s, 3H, H-18), 1.12 (s, 3H, H-19), 2.35 (m, 4H, CH_2–C═O), 2.44 (m, 4H, CH_2–C═), 2.83 (m, 1H, H-7β), 2.90 (m, 1H, H-3β), 3.24 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 4.07 (m, 4H, H-12 and H-24), 5.86 (td, J = 6.4 and 15.3 Hz, 1H, CH═), 6.01 (td, J = 6.3 Hz and 15.3 Hz, 1H, CH═); ^{13}C NMR (75 MHz, $CDCl_3$): 18.7, 21.3, 23.6, 24.5, 24.9, 27.6, 29.6, 31.7, 32.4, 33.1, 34.3, 34.7, 35.1, 36.7, 36.9, 37.1, 37.8, 41.9, 42.3, 44.7, 47.2, 51.9, 57.3, 57.9, 62.3, 69.0, 70.4, 71.6, 73.0, 74.3, 81.9, 82.5, 121.1, 126.3. HRMS (EI) for $C_{34}H_{60}O_5$ [M^+] calcd 548.4441 found 548.4446.

*2.29. Macrocycle **13a***

Yield 45 mg (92%). Oil. IR (neat) 2984, 1374, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 1.01 (s, 3H, H-18), 1.06 (d, J = 6.4 Hz, 3H, H-21), 1.16 (s, 3H, H-19), 2.24 (m, 4H, CH_2–C=), 3.12 (m, 1H, H-7β), 3.16 (m, 1H, H-3β), 3.52 (m, 4H, H-12 and H-24), 5.89 (td, J = 6.1 and 15.4 Hz, 1H, CH=), 6.04 (td, J = 6.3 Hz and 15.3 Hz, 1H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): 18.7, 20.6, 23.3, 24.1, 25.3, 28.6, 31.7, 32.6, 32.9, 33.1, 33.7, 34.2, 36.7, 37.8, 39.2, 41.6, 42.1, 44.9, 46.9, 52.4, 62.3, 65.1, 66.5, 68.9, 71.3, 77.8, 72.3, 73.9, 119.6, 126.1. HRMS (EI) for $C_{30}H_{52}O_5$ [M^+] calcd 492.3815 found 492.3819.

*2.30. Macrocycle **13b***

Yield 40 mg (90%). Oil. IR (neat) 3429, 2950, 1606, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 0.99 (s, 3H, H-18), 1.02 (d, J = 6.4 Hz, 3H, H-21), 1.10 (s, 3H, H-19), 2.14 (m, 4H, CH_2–C=), 3.22 (m, 1H, H-7β), 3.31 (m, 1H, H-3β), 4.02 (m, 8H, CH_2-O, H-12 and H-24), 5.72 (td, J = 6.1 and 15.4 Hz, 1H, CH=), 5.97 (td, J = 6.2 Hz and 15.3 Hz, 1H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): 18.4, 21.6, 23.9, 24.1, 24.7, 27.3, 29.2, 31.4, 32.0, 32.7, 33.9, 34.6, 35.2, 36.9, 37.1, 37.4, 37.9, 41.6, 43.0, 44.2, 47.1, 52.1, 63.4, 68.8, 70.6, 71.9, 73.1, 73.9, 80.8, 81.7, 119.6, 125.9. HRMS (EI) for $C_{32}H_{56}O_5$ [M^+] calcd 520.4128 found 520.4134.

*2.31. Macrocycle **23a***

Yield 80 mg (54%). Oil. IR (neat) 3280, 1730, 1220, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 0.00 (12H, s, $Si(CH_3)_2$), 0.65 (s, 3H, H-18), 0.83 (18H, s, $C(CH_3)_3$), 0.94 (3H, d, J = 6.4 Hz, H-21), 1.02 (3H, s, H-19), 3.38 (m, 1H, H-8β), 3.44 (m, 4H, CH_2–C=O), 3.55 (m, 2H, H-12β and H-3β), 3.90 (m, 4H, H-24 and H-7), 5.76 (td, J = 6.4 and 15.2 Hz, 1H, CH=), 6.02 (td, J = 6.1 Hz and 15.3 Hz, 1H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): −4.4 (2C), −3.5 (2C), 12.6, 15.3, 17.9, 18.3 (2C), 24.3, 24.7 (2C), 25.1, 26.2, 27.4, 29.8, 30.6, 31.2, 31.6, 31.9, 33.2, 35.4, 36.1, 36.3, 36.6, 37.8, 41.3, 42.1, 46.2, 47.0, 47.3, 50.7, 52.6, 65.4, 66.2, 72.5, 72.9, 76.5, 127.6, 133.9, 174.4, 174.6. HRMS (EI) for $C_{42}H_{76}O_7Si_2$ [M^+] calcd 748.5130 found 748.5135.

*2.32. Macrocycle **23b***

Yield 78 mg (50%). Oil. IR (neat) 3448, 1732, 1607, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 0.00 (12H, s, $Si(CH_3)_2$), 0.64 (s, 3H, H-18), 0.83 (18H, s, $C(CH_3)_3$), 0.92 (3H, d, J = 6.4 Hz, H-21), 1.22 (3H, s, H-19), 2.31 (m, 8H, $(CH_2)_2$–C=), 3.36 (m, 1H, H-8β), 3.42 (m, 4H, CH_2–C=O), 3.52 (m, 2H, H-12β and H-3β), 3.86 (m, 4H, H-24 and H-7), 5.48 (td, J = 6.4 and 15.4 Hz, 1H, CH=), 5.93 (td, J = 6.2 Hz and 15.3 Hz, 1H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): −4.6 (2C), −3.6 (2C), 12.8, 18.1, 18.6 (2C), 22.6, 24.3, 25.8 (2C), 26.0, 26.2, 26.7, 26.9, 29.6, 31.3, 31.9, 34.1, 34.7, 34.9, 35.5, 35.6, 35.9, 37.2, 37.4, 38.0, 40.9, 41.6, 44.5, 46.3, 47.2, 47.5, 53.5, 64.8, 68.0, 70.5, 72.5, 72.7, 128.4, 129.4, 172.1, 173.2. HRMS (EI) for $C_{44}H_{80}O_7Si_2$ [M^+] calcd 776.5443 found 776.5448.

*2.33. Macrocycle **24a***

Yield 40 mg (52%). Oil. IR (neat) 3420, 1264, 905 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 0.00 (12H, s, $Si(CH_3)_2$), 0.66 (s, 3H, H-18), 0.85 (18H, s, $C(CH_3)_3$), 1.02 (3H, d, J = 6.4 Hz, H-21), 1.08 (3H, s, H-19), 3.34 (m, 1H, H-8β), 3.43 (m, 2H, H-12β and H-3β), 3.66 (m, 4H, CH_2–O), 3.90 (m, 4H, H-24 and H-7), 5.72 (td, J = 6.3 and 15.2 Hz, 1H, CH=), 5.96 (td, J = 6.3 Hz and 15.4 Hz, 1H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): −4.6 (2C), −3.5 (2C), 12.2, 14.9, 18.1, 18.8 (2C), 24.1, 24.9 (2C), 25.4, 26.0, 27.5, 28.9, 30.1, 31.4, 31.8, 32.0, 33.3, 35.6, 36.3, 36.7, 37.2, 38.4, 39.6, 41.3, 41.7, 46.6, 47.1, 51.2, 52.3, 66.2, 68.1, 70.6, 70.9, 72.4, 73.1, 76.4, 127.4, 129.9. HRMS (EI) for $C_{42}H_{80}O_5Si_2$ [M^+] calcd 720.5544 found 720.5549.

*2.34. Macrocycle **24b***

Yield 35 mg (46%). Oil. IR (neat) 3435, 2990, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 0.00 (12H, s, $Si(CH_3)_2$), 0.66 (s, 3H, H-18), 0.89 (18H, s, $C(CH_3)_3$), 0.98 (3H, d, J = 6.4 Hz, H-21), 1.17 (3H, s, H-19), 2.31 (m, 8H, $(CH_2)_2$–C=), 3.41 (m, 1H, H-8β), 3.48 (m, 2H, H-12β and H-3β), 3.67 (m, 4H, CH_2–O), 3.89 (m, 4H, H-24 and H-7), 5.42 (td, J = 6.1 and 15.4 Hz, 1H, CH=), 5.87 (td, J = 6.2 Hz and 15.3 Hz, 1H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): −4.9 (2C), −3.6 (2C), 12.4, 18.7, 19.1 (2C), 23.1, 24.5 (2C), 25.6, 25.9, 26.4, 26.8, 27.1, 29.2, 31.4, 32.0, 34.1, 34.3, 34.9, 35.1, 35.8, 36.6, 37.4, 37.5, 38.6, 39.8, 41.3, 43.2, 45.9, 46.2, 47.4, 54.1, 64.2, 67.9, 69.9, 70.5, 71.1, 72.8, 73.2, 128.1, 129.6. HRMS (EI) for $C_{44}H_{84}O_5Si_2$ [M^+] calcd 748.5857 found 748.5861.

*2.35. Macrocycle **25a***

Yield 28 mg (95%). Oil. IR (neat) 3410, 2940, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 0.64 (s, 3H, H-18), 1.04 (3H, d, J = 6.4 Hz, H-21), 1.12 (3H, s, H-19), 3.32 (m, 2H, H-12β and H-3β), 3.42 (m, 1H, H-8β), 3.48 (m, 4H, CH_2–O), 3.72 (m, 4H, H-24 and H-7), 5.67 (td, J = 6.4 and 15.3 Hz, 1H, CH=), 5.89 (td, J = 6.3 Hz and 15.4 Hz, 1H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): 14.1, 17.9, 23.6, 24.4, 27.1, 27.8, 29.1, 31.0, 31.6, 31.7, 32.4, 33.7, 34.8, 36.2, 36.9, 37.6, 38.9, 45.7, 47.8, 51.6, 52.1, 65.8, 67.9, 70.4, 71.2, 72.6, 73.4, 75.9, 126.9, 129.1. HRMS (EI) for $C_{30}H_{52}O_5$ [M^+] calcd 492.3815 found 492.3821.

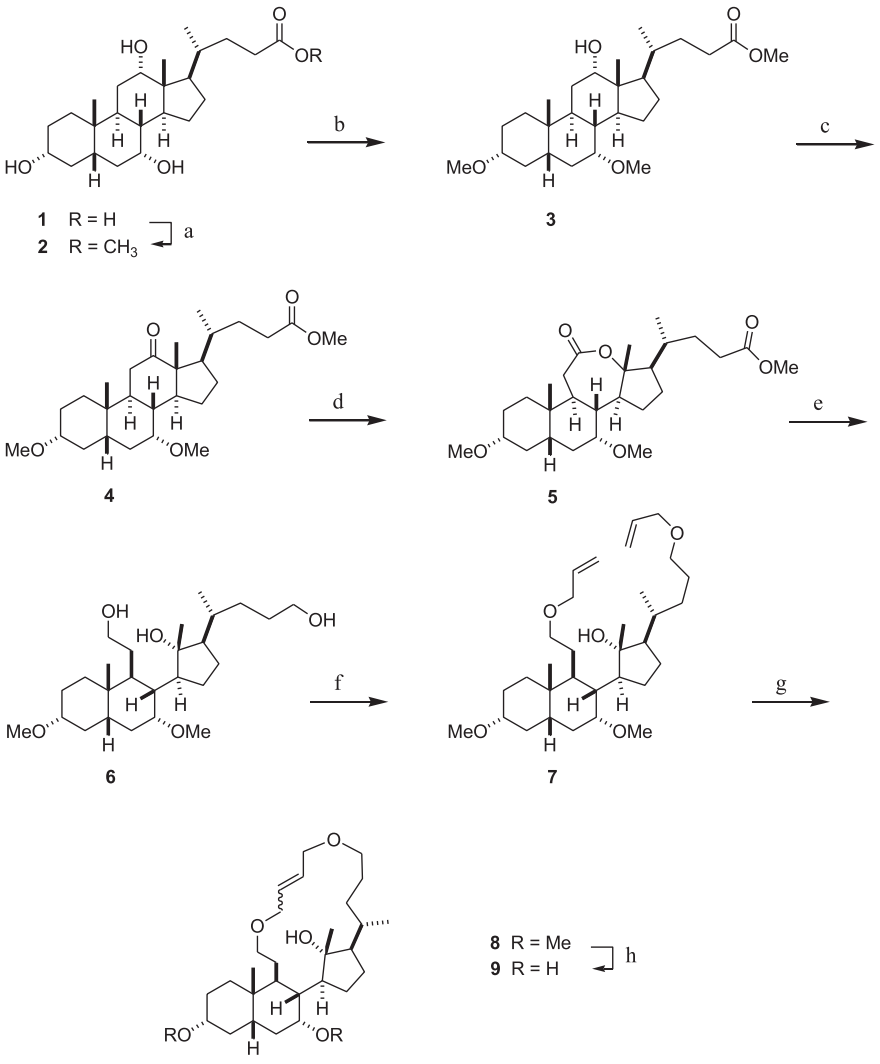
*2.36. Macrocycle **25b***

Yield 25 mg (96%). Oil. IR (neat) 3386, 1070, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer): 0.67 (s, 3H, H-18), 0.99 (3H, d, J = 6.4 Hz, H-21), 1.11 (3H, s, H-19), 2.16 (m, 8H, $(CH_2)_2$–C=), 3.21 (m, 2H, H-12β and H-3β), 3.39 (m, 4H, CH_2–O), 3.45 (m, 1H, H-8β), 3.67 (m, 4H, H-24 and H-7), 5.48 (td, J = 6.2 and 15.4 Hz, 1H, CH=), 5.89 (td, J = 6.2 Hz and 15.3 Hz, 1H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): 12.9, 18.4, 23.3, 24.8, 25.9, 27.1, 29.3, 30.7, 32.4, 33.7, 34.1, 34.9, 35.5, 35.9, 36.2, 37.1, 38.0, 38.9, 42.2, 45.6, 46.3, 47.1, 53.9, 64.6, 68.5, 69.1, 70.7, 71.4, 72.6, 73.7, 127.2, 129.8. HRMS (EI) for $C_{32}H_{56}O_5$ [M^+] calcd 520.4128 found 520.4132.

3. Results and discussion

Olefin metathesis has become one of the most powerful and attractive tools for the formation of carbon-carbon double bonds and is widely used in organic synthesis. The spectacular improvements in this reaction achieved over the last two decades are well known to most chemists. An increasing number of papers devoted to applications of olefin metathesis in the synthesis of natural products are observed [38–44]. Although ring-closing metathesis (RCM) is known to be a powerful tool for the preparation of macrocycles [45–49], in the field of steroid chemistry, only few syntheses have been reported based on metathesis reactions [50].

For some years, we have been interested to develop new synthetic approaches to prepare secosteroidal molecules. We recently described a simple preparation of 12,13- (Scheme 2) and 7,8-secosteroids (Scheme 4) possessing a macrocycle using a ring-closing metathesis reaction as the key step [51]. Indeed, this combination



Reaction conditions : (a) MeOH, PTSA, Δ, 2 h, 99%; (b) CH_3I, NaH, THF, r.t., 94%; (c) PCC, MW,5 min, 70%; (d) *m*-CPBA, PTSA, CH_2Cl_2, r.t., 24 h, 98%; (e) $LiAlH_4$, THF, 0 °C to r.t., 12 h, 88%; (f) allyl bromide, KH, DMF, 0 °C to r.t., 12 h, 58%; (g) Grubbs-II catalyst (20 mol%), CH_2Cl_2, r.t., 12 h, 65%; (h) $ISi(CH_3)_3$, $CHCl_3$, r.t., 24 h, 92%.

Scheme 2. Synthesis of a 12,13-secosteroidal macrocycle **9** from cholic acid through 8 steps sequence.

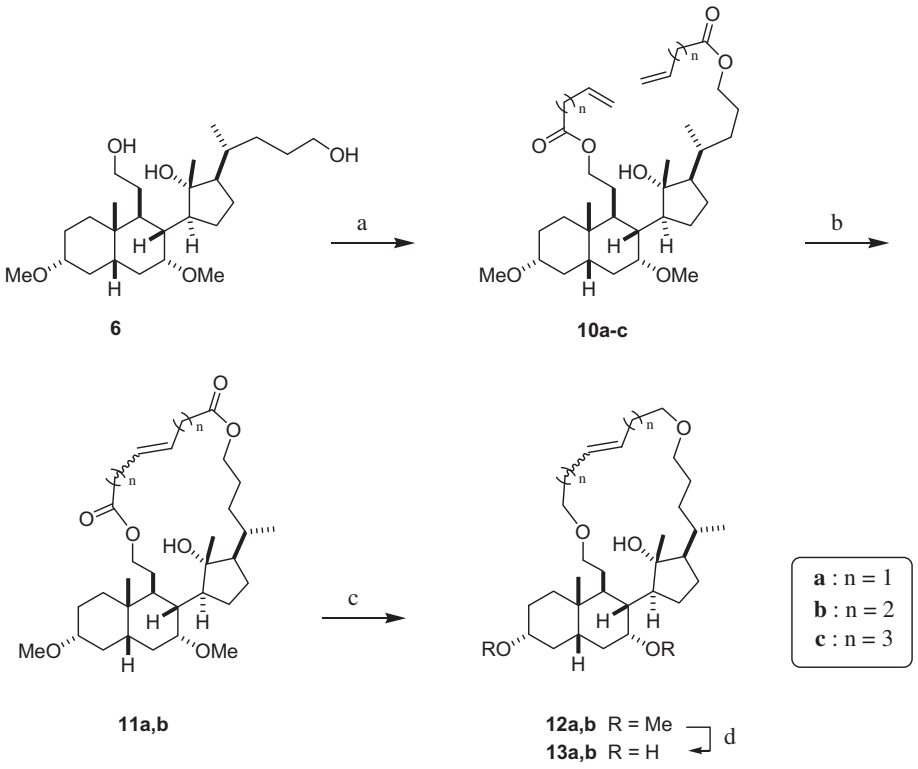
of secocholanic skeleton with varied types of macrocycles, produces high levels of skeletal diversity and complexity.

Our strategy is based on a sequential ring-expansion/ring-opening and on a ring closing metathesis reaction [51]. In the two previously described syntheses (Schemes 2 and 4), we prepared the RCM substrates from cholic acid, a commercial bile acid both inexpensive and readily available. In the case of 12,13-secosteroidal macrocycles matching a *cis* A/B ring junction, the key reactions are depicted in Scheme 2. Simple esterification of cholic acid **1** led to methyl cholate [52], which was methylated with methyl iodide-sodium hydride in THF affording methyl 3α,7α-dimethoxy cholate **3** in a yield of 94%. Simultaneous protection of the secondary hydroxyl groups at C-3 and C-7 was needed prior to the reductive opening of the lactone ring. Microwave (MW) [53] irradiation of **3** with pyridinium chlorochromate furnished ketone **4** very quickly, in a few minutes, and in 70% yield. Baeyer-Villiger oxidation of ketocholane **4** led to lactone **5** as the single regioisomer, as a result of a higher migration aptitude of the quaternary C-13 compared to the secondary C-11. Next, the simultaneous reduction of both the lactone moiety on ring C and the ester function at C-24 afforded the diprotected pentahydroxysecocholane **6** in 88% yield. Diallylation of primary alcohols at C-24 and C-12 produced the corresponding diallyl adduct **7** in moderate yield (58%).

The key step of the synthesis, the RCM reaction of **7** was accomplished efficiently with the use of a catalytic amount of Grubbs-II catalyst (20 mol%) in toluene at 80 °C providing secosteroid **8** in good yield (65%). However, the reaction was not stereoselective, a mixture of geometric isomers **8** was obtained with the E isomer. The structure of this macrocycle was completely characterized by NMR (400 MHz) and mass spectroscopy methods (see experimental part). A 8:2 ratio of isomers was obtained with the *trans* (J = 15.2 Hz) isomer prevailing over the *cis* (J = 10.6 Hz) isomer.

Finally, removal of methoxy groups of **8** was carried out with trimethylsilyl iodide [33] to afford the desired compound **9** in 92% yield.

Encouraged by this result and to show that this ring enlargement is generally applicable, different types of olefins were subjected to metathesis reaction (Scheme 3 and Table 1). We present now results of our further study on metathesis of secosteroidal esters with various sized acid chain (C_4, C_5 and C_6). Dienes **10a-c** were prepared in high yields by reaction of steroid **6** with alkenoic acids in the presence of DCC and DMAP. All esters



Reaction conditions : (a) CH_2=$CH(CH_2)_n$COOH, DCC, DMAP, 0 °C to r.t., 12 h; (b) Grubbs-II catalyst (20 mol%), see table 1; (c) $NaBH_4$, BF_3.Et_2O, THF-diglyme, 0 °C, 4 h; (d) $ISi(CH_3)_3$, $CHCl_3$, r.t., 24 h.

Scheme 3. Synthesis of 12,13-secosteroidal macrocycles **13** from diprotected secosteroid **6**.

Table 1
Metathesis reactions *via* Scheme 3.

Entry	Olefin	*n*	Cat[a]	Condition	11: yield (%)
1	**10a**	1	A	CH_2Cl_2, rt, 24 h	18
2	**10a**	1	B	CH_2Cl_2, rt, 24 h	29
3	**10a**	1	B	MePh, Δ, 4 h	56
4	**10b**	2	A	CH_2Cl_2, rt, 24 h	11
5	**10b**	2	B	CH_2Cl_2, rt, 24 h	23
6	**10b**	2	B	MePh, Δ, 4 h	48
7	**10c**	3	A	CH_2Cl_2, rt, 24 h	–
8	**10c**	3	B	CH_2Cl_2, rt, 24 h	–
9	**10c**	3	B	MePh, Δ, 4 h	–

[a] A = $RuCl_2(PCy_3)_2$ = CHCHCMe$_2$; B = (IMES)$(PCy)_3Cl_2Ru$ = CHPh; IMES = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene.

obtained were found to be stable and were subjected to RCM reactions. According to the literature, synthesis of unsaturated lactones through RCM has been accomplished using either Grubbs, first or second generation, or Hoveyda catalyst.

We decided to test two commercially available metathesis promoters: Grubbs first-generation (GI) and Grubbs second-generation GII (Table 1). In all cases, the Grubbs catalyst of second generation was more efficient than the first generation. We carried out the first experiments under relatively mild conditions: 20 mol% of catalyst in dry and degassed dichloromethane at room temperature. Using these experimental conditions, we observed fair yields for **11a** and **11b**. The yields of the cyclization products of **10a** and **10b** were improved by increasing the temperature (Table 1, entries 3 and 6). Although many successful applications of RCM to the synthesis of macrocycles with $n = 1$ and $n = 2$, in the case of $n = 3$, the RCM did not occur and the remaining material was mainly the unreacted starting diene **10c**.

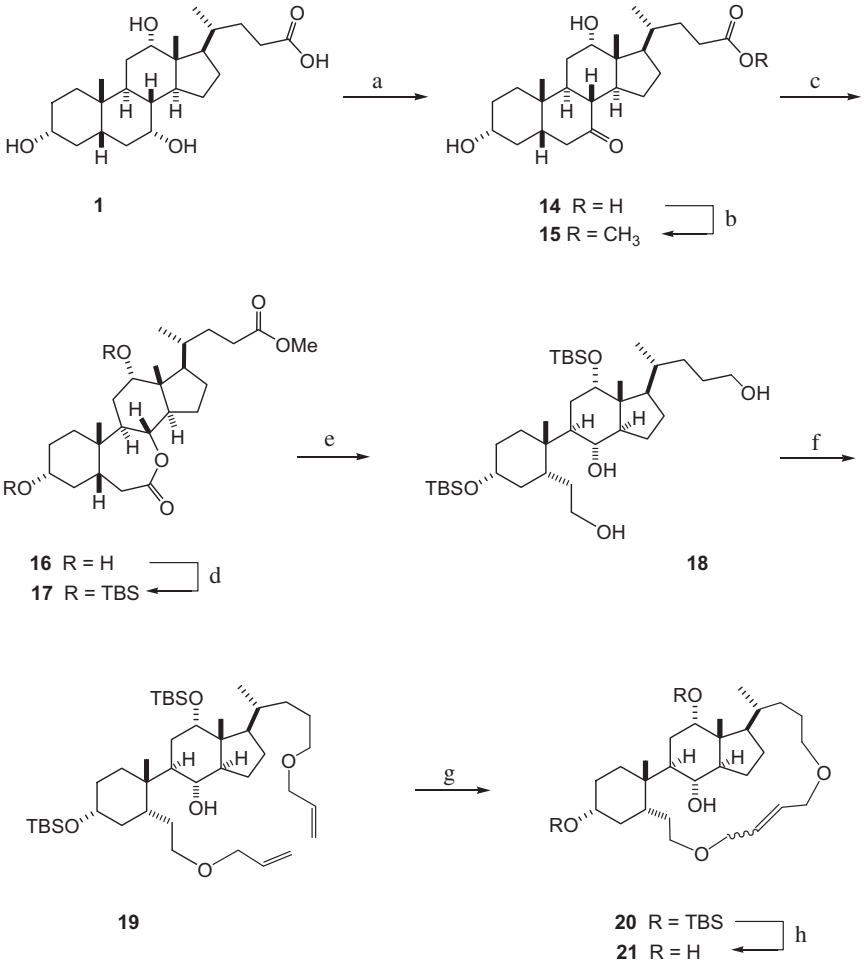
Otherwise, the reaction was not stereoselective. All metathesis products were obtained as mixtures of geometric *E*/*Z*-isomers with the *E* isomer predominating. The structure of these new secosteroidal macrocycles **11a-b** was completely characterized by NMR (400 MHz) and mass spectroscopic methods (see experimental part).

In the following step, in order to obtain ether-linked macrocycles as for compound **9** ($n = 0$, see Scheme 2), we reduced esters **11a** and **11b** to the corresponding ethers **12a** and **12b**, was carried out using sodium borohydride and boron trifluoride, in diglyme-tetrahydrofuran at 0 °C during 4 h. Thus, in the two cases, reduction according to the Pettit and Piatak procedure [54], afforded the expected macrocycle derivatives **12a** and **12b** in satisfactory yields : 56% for **12a** and 48% for **12b**.

Finally, removal of methoxy groups of macrocycles **12a** and **12b** was carried out with trimethylsilyl iodide [55,56] to afford the desired compounds **13a** and **13b** in good yields. The problem of formation of isomers can be, of course, overcome by hydrogenation of the newly formed double bond.

As a continuation of our synthetic and stereochemical studies on secosteroidal systems containing a macrocycle, a similar strategy was used to obtain 7,8-secosteroidal macrocycles (Scheme 4). The regioselective oxidation of the hydroxyl group at C-7 was performed with NBS [57]. The resulting 7-keto derivative **14** was then converted into cholate **15** in good yield (95% yield over two steps).

As expected, the Baeyer–Villiger oxidation of ketocholane **15** furnished exclusively regioisomer **16**, as a result of the favored



Reaction conditions : (a) NBS, H_2O, $NaHCO_3$, 12 h at r.t. then 2h at 80-85 °C, 95%; (b) MeOH, PTSA, Δ, 2h, 100%; (c) *m*-CPBA, PTSA, CH_2Cl_2, r.t., 24 h, 82%; (d) TBDMSCl, imidazole, DMF, r.t., 12 h, 91%; (e) $LiAlH_4$,THF, 0 °C to r.t., 12 h, 90%; (f) allyl bromide, KH, DMF, 0 °C to r.t., 12 h, 56%; (g) Grubbs-II catalyst (20 mol%), CH_2Cl_2, r.t., 12 h, 90%; (h) TBAF, THF, r.t.,12 h, 92%.

Scheme 4. Synthesis of a 7,8-secosteroidal macrocycle **21** from cholic acid through 8 steps sequence.

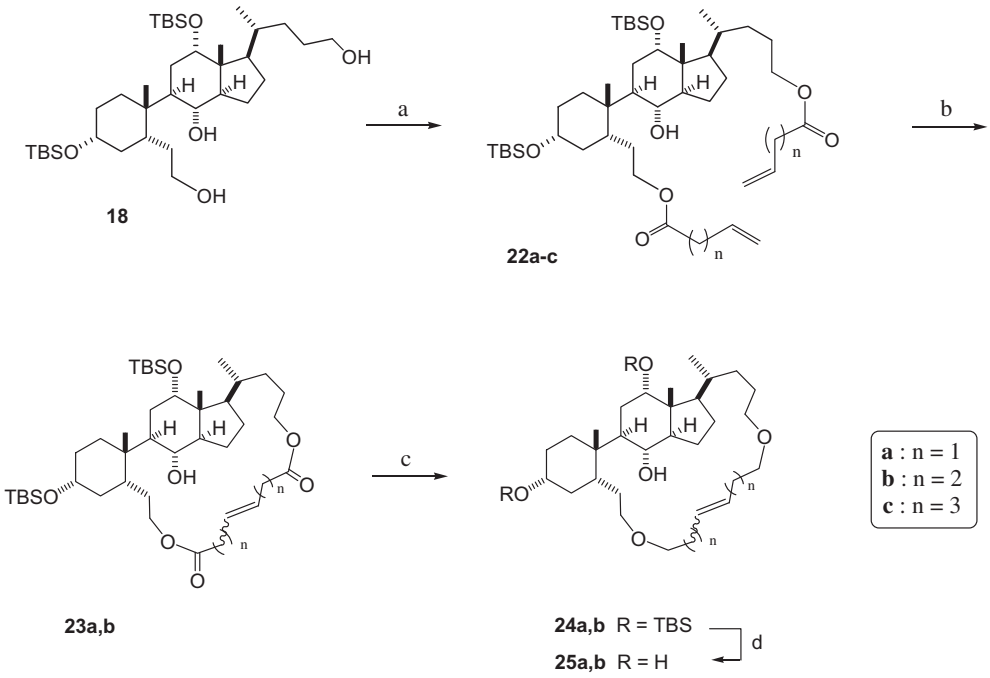
migration of the tertiary C-8 compared to the secondary C-6. Consecutively, a reaction sequence consisted in TBDMS protection of OH functionalities, followed by the reductive opening of the lactone ring with simultaneous reduction of the ester function at C-24 and finally regioselective diallylation reaction of primary alcohols at C-24 and C-7 led to the diallyl secocholane **19** in 38% overall yield (over four steps). The RCM was promoted by the second generation Grubbs' catalyst and the reaction was very efficient. Using the same conditions as described above for **9**, we obtained the macrocyclic product **20** in 90% yield. Here too, this latter **20** was completely characterized by NMR and mass spectroscopic methods (see experimental part). The E/Z 9:1 ratio observed in the ^{1}H NMR spectrum of the crude substance was strongly in favor of the *E*-isomer (J = 15.6 Hz) with small amounts of sterically less favored *Z*-double bond (J = 10.4 Hz).

The 3- and 12-TBS ethers on the A and C rings of **20** were deprotected in a standard manner to afford the corresponding secosteroidal alcohol **21** in good yield.

We have then turned our attention toward the synthesis of new macrocycles by introducing ester functionalities on the secosteroidal alcohol **18** (Scheme 5). An interesting feature of this methodology is the possibility for the expansion of the ring size by adjusting the length of the acid source used for the synthesis of RCM precursors **22**.

Thus, three alkenoates (compounds **22a-c**) were prepared in good yields by reaction of diprotected pentadihydroxysecocholane **18** with alkenoic acids in presence of DCC and DMAP. Here too, esters **22a-c** were found to be stable and were subjected to RCM reactions using Grubbs first-generation (GI) or second-generation (GII) as catalyst (see Table 2).

It is worth pointing out similar results with the work we described above for the synthesis of 12,13-secosteroidal macrocycles. Indeed, the cyclization of **22** was observed for n = 1 and n = 2 but without any success for n = 3. Here too, the remaining material was mainly the unreacted starting diene **22c**. It is interesting to note that the yields and the isomer ratio observed for **23a** and **23b** are exactly or quite the same as those reported for the 12,13-secosteroidal series. Otherwise, in some experiments, the reaction temperature was raised to 40 °C without significant change of reaction course. Only the use of the catalyst of second generation (Grubbs II) at 80 °C in dry and degassed toluene proved effective in the RCM products formation **23a** or **23b** (Table 2,



Reaction conditions : (a) CH_2=CH(CH_2)$_n$COOH, DCC, DMAP, 0 °C to r.t., 12 h; (b) Grubbs-II catalyst (20 mol%), see table 2; (c) $NaBH_4$, BF_3.Et_2O, THF-diglyme, 0 °C, 4 h; (d) TBAF, THF, r.t.,12 h.

Scheme 5. Synthesis of 7,8-secosteroidal macrocycles **25** from diprotected secosteroid **18**.

Table 2
Metathesis reactions *via* Scheme 5.

Entry	Olefin	*n*	Cat[a]	Condition	23: yield (%)
1	**22a**	1	A	CH_2Cl_2, rt, 24 h	12
2	**22a**	1	B	CH_2Cl_2, rt, 24 h	26
3	**22a**	1	B	MePh, Δ, 4 h	54
4	**22b**	2	A	CH_2Cl_2, rt, 24 h	9
5	**22b**	2	B	CH_2Cl_2, rt, 24 h	24
6	**22b**	2	B	MePh, Δ, 4 h	50
7	**22c**	3	A	CH_2Cl_2, rt, 24 h	–
8	**22c**	3	B	CH_2Cl_2, rt, 24 h	–
9	**22c**	3	B	MePh, Δ, 4 h	–

[a] A = $RuCl_2(PCy_3)_2$=CHCHCMe$_2$; B = (IMES)$(PCy)_3Cl_2$Ru=CHPh; IMES = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene.

entries 3 and 6). The influence of other reaction conditions on the reaction course, e.g. dilution (tested concentration: 0.5–1.5 mM), mode of reagent addition, appeared to be much less important.

Further synthesis of macrocycles consisted of reduction of the obtained lactones (**23a**, **23b**) with a metal hydride. As described above for the 12,13-secosteroidal series, reduction of **23a** and **23b** using sodium borohydride and boron trifluoride in diglyme-tetrahydrofuran [54] afforded the corresponding ethers **24a** and **24b** in 52% and 46% yield respectively.

In the final step, the 3α- and 12α-hydroxyl groups in compounds **24a** and **24b** were deprotected with TBAF in a standart manner to afford the corresponding alcohols **25a** and **25b** in excellent yield (see experimental part).

In conclusion, in this paper, it was proven that the RCM strategy can be successfully applied to the synthesis of diverse secosteroids from commercially available cholic acid. The key steps of this synthesis are an oxidative ring-expansion/ring-opening sequence and a ring-closing metathesis. The subsequent reduction of the obtained RCM products afforded new macrocycle derivatives. 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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