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A click chemistry approach to secosteroidal macrocycles

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ABSTRACT

A new synthetic pathway towards secosteroidal macrocycles was described *via* a reaction of cycloaddition as the key step. The characteristic ^{1}H and ^{13}C NMR spectroscopic features of the synthesized compounds are reported.

1. Introduction

Secosteroids have attracted considerable interest because of the broad range of biological activities of many naturally occurring representatives, such as vitamins D [1], with 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 [11–18]. It is evident that the higher conformational flexibility of seco steroids in comparison with normal steroids may result in novel, pharmaceutically useful compounds.

Moreover, [1,2,3]-triazoles are important class of five-membered nitrogen heterocycles. They have been reported to have important biological activities, including anti-HIV [19], anti-tumor [20], anti-bacterial [21], and anti-tuberculosis [22], and can also act as glycosidase [23–24], tyronase [25], and serine hydrolase [26] inhibitors.

The incidence of life-threatening fungal infections has tremendously increased in the last two decades due to greater use of immunosuppressive drugs, prolonged use of broad spectrum antibiotics, widespread use of indwelling catheters, and also in cancer and AIDS patients. The presently marketed antifungal and antibacterial drugs are either highly toxic or becoming ineffective due to the appearance of resistant strains. This necessitates continuing research into new classes of antimicrobial agents. 1,2,3-Triazole-containing molecules is one of these classes.

1,2,3-Triazole moieties are attractive connecting units because they are stable to metabolic degradation and capable of hydrogen bonding, which can be favorable in the binding of biomolecular targets and can improve the solubility [27,28]. The 1,2,3-triazole moiety does not occur in nature, although the synthetic molecules that contain 1,2,3-triazole units show diverse biological activities. The importance of triazolic compounds in medicinal chemistry is undeniable. Contrary to other azaheterocycles, the 1,2,3-triazole ring is not protonated at physiological pH because of its poor basicity.

Recently, Pore and co-workers [29,30] reported the synthesis of novel 1,2,3-triazole-linked β-lactam-bile acid conjugates **A** and some dimeric compounds **B** by 1,3-dipolar cycloaddition reaction of azido β-lactam and terminal alkyne of bile acids by using a click reaction (Scheme 1). Most of the compounds exhibited significant antifungal and moderate antibacterial activity against all the tested strains.

The unique chemistry behavior of this moiety aroused the chemist's interest, ranging from a synthetic point of view to the context of biological and pharmacological application.

So, for some years, we have been interested to develop new synthetic approaches to prepare secosteroidal molecules. Herein, we report a new and simple preparation of secocholanic steroids possessing a macrocycle and a triazole unit in their structure. Indeed, this combination of secocholanic skeleton with varied types of macrocycles, produces high levels of skeletal diversity and complexity. Additionally, there are no example, which describe the application of the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction for the synthesis of secosteroids.

We report here the full details of these syntheses.

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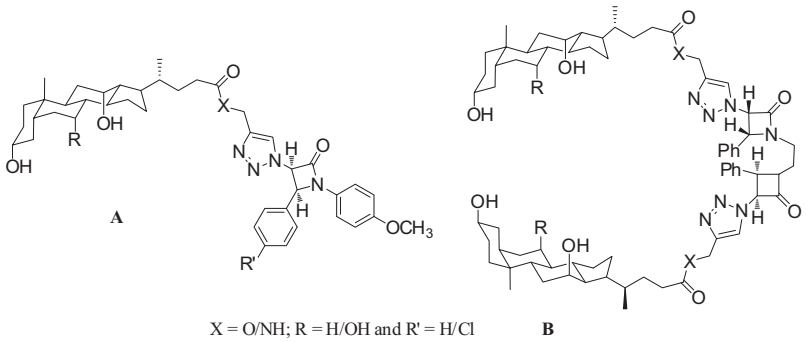

Scheme 1. Bile acid derivatives with biological activities.

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 **14** and **15** were prepared according to the previously described procedure [31]. The nomenclature used for the steroids is not the nomenclature used by Chemical Abstracts [32,33].

2.1. Propargyl 3α,7α,12α-trihydroxy-5β-cholan-24-oate (2)

A solution of cholic acid **1** (320 mg, 0.78 mmol), propargyl bromide (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 propargyl cholate **2** (260 mg, 75%) as an oil. IR (neat) 3280, 1736, 1220, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 0.68 (s, 3H, H-18), 0.98 (d, J = 6.4 Hz, 3H, H-21), 1.18 (s, 3H, H-19), 2.48 (t, J = 2.4 Hz, 1H, H-27), 2.87 (m, 1H, H-7), 2.92 (m, 1H, H-3), 3.42 (m, 1H, H-12), 4.67 (d, J = 2.8 Hz, 1H, H-25); ^{13}C NMR (75 MHz, $CDCl_3$): 17.4, 20.4, 24.3, 27.7, 29.2, 29.8, 31.6, 34.7, 34.6, 35.0, 35.9, 37.4, 40.6, 45.4, 46.6, 49.6, 51.8, 53.5, 57.6, 63.4, 68.3, 74.8, 76.5, 77.9, 79.8, 79.9, 173.4. HRMS (EI) for $C_{27}H_{42}O_5$ [M$^+$] calcd 446.3032 found 446.3036.

2.2. Propargyl 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 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 **3** (4.6 g, 86%) as a white solid. mp = 132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 0.62 (s, 3H, H-18), 0.83 (d, J = 6.5, 3H, H-21), 0.86 (s, 3H, H-19), 2.46 (t, J = 2.4 Hz, 1H, H-27), 2.94 (m, 1H, H-3), 3.14 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 3.21 (m, 1H, H-7), 3.29 (m, 1H, H-12), 4.76 (d, J = 2.8 Hz, 1H, H-25); ^{13}C NMR (75 MHz, $CDCl_3$): 17.7, 19.9, 24.8, 27.6, 28.8, 29.2, 31.4, 34.2, 34.7, 35.6, 36.9, 37.1, 40.2, 44.4, 45.6, 49.1, 52.0, 53.4, 56.9, 57.2, 58.0, 63.1, 67.9, 73.6, 76.2, 77.8, 79.1, 82.3, 173.1. HRMS (EI) for $C_{29}H_{46}O_5$ [M$^+$] calcd 474.3345 found 474.3348.

2.3. Propionyl ether of 3α,7α-dimethoxy-12α-hydroxy-5β-cholane (4)

A flask equipped with a magnetic stirring bar, an argon outlet and a condenser was charged with $NaBH_4$ (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), ester **3** (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 $MgSO_4$, filtered and then concentrated under vacuum. The residue was chromatographed on silica gel (Et_2O–petroleum ether 1:1). Yield 46 mg (56%). Oil IR (neat) 3280, 1220, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 0.66 (s, 3H, H-18), 0.81 (d, J = 6.5, 3H, H-21), 0.92 (s, 3H, H-19), 2.42 (t, J = 2.4 Hz, 1H, H-27), 2.89 (m, 1H, H-3), 3.16 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 3.24 (m, 1H, H-7), 3.32 (m, 1H, H-12), 4.27 (d, J = 2.6 Hz, 1H, H-25); ^{13}C NMR (75 MHz, $CDCl_3$): 17.4, 20.1, 24.7, 27.9, 29.1, 30.6, 32.7, 33.9, 34.6, 35.8, 37.1, 37.4, 40.8, 43.4, 45.1, 49.3, 51.4, 52.8, 57.1, 57.4, 59.0, 62.7, 67.4, 70.2, 72.6, 74.4, 76.9, 78.1, 80.3. HRMS (EI) for $C_{29}H_{48}O_4$ [M$^+$] calcd 460.3553 found 460.3559.

2.4. Propionyl ether of 3α,7α-dimethoxy-12-oxo-5β-cholane (5)

Alcohol **4** (1 g, 2.17 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. 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 0.68 g (68% yield) of 12-oxo steroid **5** as an oil. IR (neat) 3236, 1511 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 0.72 (s, 3H, H-18), 0.86 (d, J = 6.4, 3H, H-21), 0.91 (s, 3H, H-19), 2.47 (t, J = 2.1 Hz, 1H, H-27), 2.86 (m, 1H, H-3), 3.17 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 3.26 (m, 1H, H-7), 4.16 (d, J = 2.3 Hz, 1H, H-25); ^{13}C NMR (75 MHz, $CDCl_3$): 16.9, 20.3, 23.6, 27.4, 29.3, 30.1, 32.6, 33.4, 34.1, 36.2, 37.3, 38.4, 41.5, 43.6, 44.9, 49.6, 51.7, 52.1, 56.8, 57.9, 59.2, 61.9, 66.4, 69.9, 72.3, 75.7, 79.0, 81.1, 214.9. HRMS (EI) for $C_{29}H_{46}O_4$ [M$^+$] calcd 458.3396 found 458.3400.