Article

J. Mex. Chem. Soc. **2006**, *50(4)*, 160-163

ISSN 1870-249X

Preparation and Characterization of Rosmarinecine Derivatives

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Recibido el 8 de agosto del 2006; aceptado el 6 de octubre de 2006.

Abstract. This work describes the synthesis of 8-*tert*-butyldimethylsilyloxy- (**3**), 2,8-bis(*tert*-butyldimethylsilyloxy)- (**4**) 2-mesyloxy-8-*tert*-butyldimethylsilyloxy- (**5**), and 2-tosyloxyrosmarinecine (**6**) from selective protection of the different hydroxyl groups of rosmarinecine **2**, which was obtained by hydrolysis of rosmarinine **1**. The rosmarinine **1** naturally occuring was isolated in good yields (0.66%) from *Senecio callosus.* The chemoselectivity of the silylation of the hydroxyl groups at position C-2 and C-8 of **2** was controlled by the time of the reaction, which exhibited a higher reactivity for primary hydroxyl than secondary hydroxyl group, as well as the stereochemistry of the group at 1 position, which is *trans* and *cis* to the hydroxyl groups at 2 and 7 positions, respectively, where the steric efffect of hydroxyl group at 7 position is evidenced and possible effect of the solvent. The compounds were characterized by ^{1}H, ^{13}C NMR, ^{1}H-^{1}H COSY, HETCOR spectra, infrared and mass spectrometry.
Keywords: Rosmarinecine derivatives, Hydroxypyrrolizidine, Pyrrolizidine, Alkaloids, Spectroscopy.

Resumen. Este trabajo describe la síntesis de 8-*tert*-butildimetilsililoxi- (**3**), 2,8-bis(*tert*-butildimetilsililoxi)- (**4**) 2-mesiloxi-8-*tert*-butildimetilsililoxi- **(5)** y 2-tosiloxirosmarinecina (**6**) a partir de la protección selectiva de los diferentes grupos hidroxilo de la rosmarinecina **2**, la cual se obtiene por hidrólisis de la rosmarinina **1**. La rosmarinina **1** que se encuentra naturalmente se aisló en buen rendimiento (0.66%) de *Senecio callosus.* La quimioselectividad de la sililación de los grupos hidroxilo en la posiciones C-2 y C-8 de **2** fue controlada por el tiempo de reacción, el cual mostró mayor reactividad del grupo hidroxilo primario que el secundario, así como la estereoquímica del grupo en la posición 1, el cual se encuentra *trans* y *cis* a los grupos hidroxilos en las posiciones 2 y 7, respectivamente, donde el efecto estérico del grupo hidroxilo en la posición 7 es evidenciado y posible efecto del disolvente. Los compuestos fueron caracterizados por espectroscopia de RMN de ^{1}H, ^{13}C, ^{1}H-^{1}H COSY, HETCOR, infrarrojo y espectrometría de masas.
Palabras clave: Derivados de rosmarinecina, Hidroxipirrolizidina, Pirrolizidina, Alcaloides, Espectroscopía.

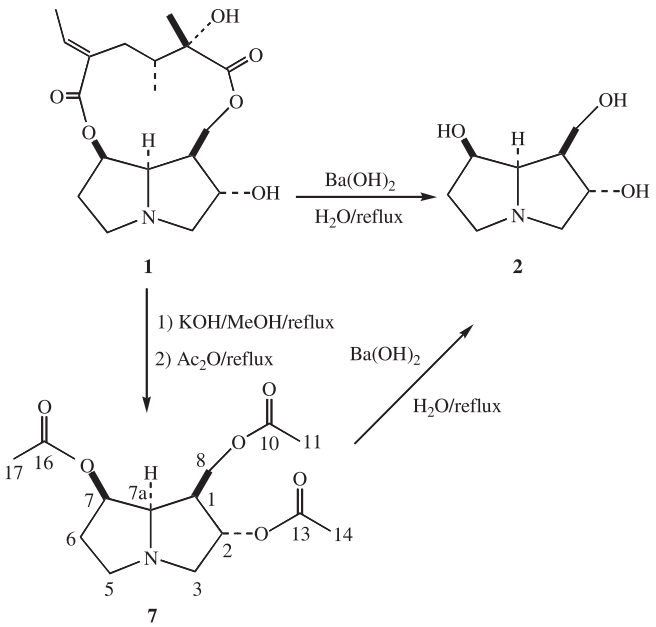
Introduction

Polyhydroxypyrrolizidine alkaloids have attracted considerable attention due to their selective inhibiting activity of glycosidases [1], this has stimulated research on the synthesis of natural polyhydroxypirrolizidine alkaloids and analogues [2-6] as potential agents against cancer [7,8] and viral infections [9,10].

In continuation with our studies on polyhydroxypyrrolizidine alkaloids [6] obtained from *Senecio callosus* [11], we describe herein the synthesis of rosmarinecine derivatives **3** to **6**, which can be precursors of new polyhydroxypyrrolizidines due to their regioselective preparation, where one or two hydroxyl groups not protected could be functionalized. All compounds were characterized by spectroscopic methods, as well as accomplished by comparison of their spectral features with those reported in literature [6].

Results and Discussion

Rosmarinine **1** was hydrolyzed by two alternative routes (Scheme 1), initially this was achieved by basic hydrolysis followed by acetylation to give 2,7,8-triacetylrosmarinecine (**7**) followed by treatment with $Ba(OH)_2$ to give **2** in 80% yield. The second method involved direct hydrolysis of rosmarinine **1** with $Ba(OH)_2$ producing **2** in 90% yield, which was development to get a short method. In both cases, the yield of the alkaloid **2** was higher than the total synthesis reported [13,14] and the ^{1}H and ^{13}C NMR data are in agreement with those described in the literature [13].



Scheme 1. Synthesis of rosmarinecine (**2**).

Alkaloid **7** has been reported [12], however, its ^{1}H and ^{13}C NMR data are not described in the literature and they are included in the experimental part.

The synthesis of 8-*tert*-butyldimethylsilyloxy- (**3**), 2,8-bis(*tert*-butyldimethylsilyloxy)- (**4**) 2-mesyloxy-8-*tert*-butyldimethylsilyloxy- (**5**) and 2-tosyloxyrosmarinecine (**6**) was carried out as shown in Scheme 2.

Reaction of **2** with TDMSCl in DMF in the presence of Et_3N and DMPA by stirring 3 h under N_2 at room temperature and treated with NaOH aq leads to chemoselective protection of the primary alcohol at position 8 to give **3**. If the same reaction is allowed to proceed for 24 h further the secondary hydroxyl group at position 2 led to 2,8-disilyloxy derivative **4**.

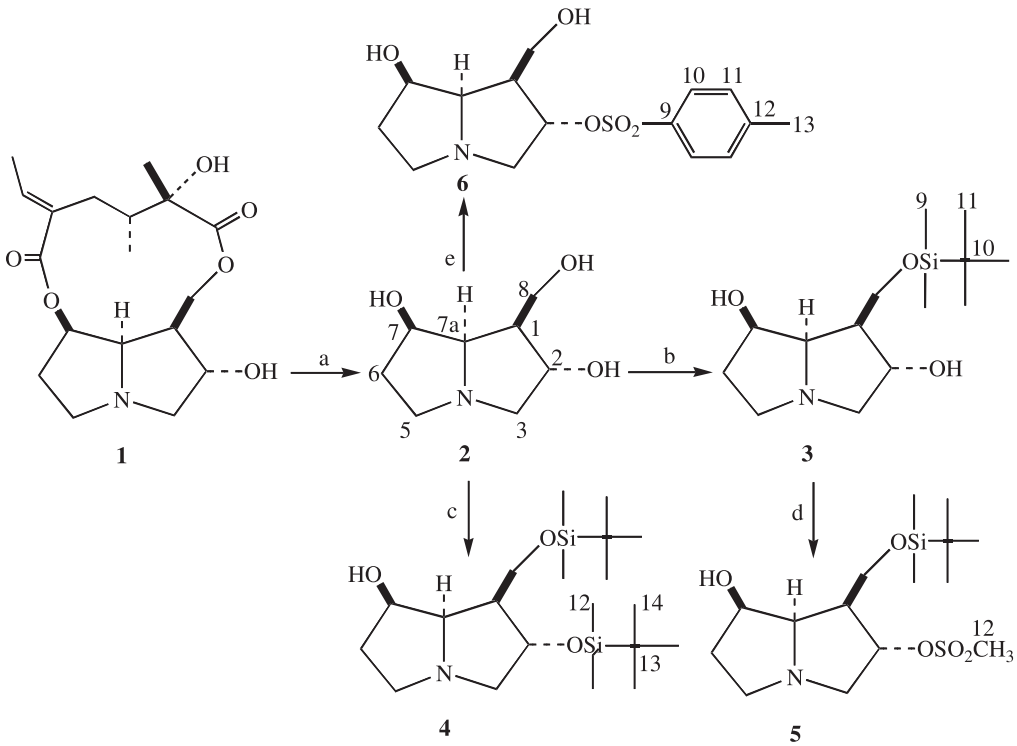
The chemoselectivity of the substitution reaction of the hydroxyl group at C-8 can be due to that primary alcohols are more reactive than secondary one.

Therefore, the selective protection of secondary hydroxyl group at C-2 with respect to that at C-7 can be attributed to that at C-2 is *trans* to the substituent at position 1 avoiding the steric effect, while hydroxyl group at C-7 is *cis* to the substituent at position 1, which could increase that effect. On another hand, the effect of DMF, being a polar solvent could avoid the intramolecular hydrogen bonds between the hydroxyl groups at C-7 and C-8, increasing the reactivity of hydroxyl group at C-8. The ^{1}H NMR spectrum of **3** showed among the characteristic signals of the alkaloid, two additional singlets for six and nine protons at δ 0.13 and 0.92, respectively, assigned to the two methyl groups and three methyl groups of the *tert*-butyl bonded to the silicon atom. The ^{13}C NMR spectrum of **3** showed a signal at δ –5.7 ppm due to carbons bonded to the Si atom, the signal at δ 25.9 was assigned to the *tert*-butyl Si carbons, while the quaternary carbon bonded to Si atom appeared at δ 18.3.

Similarly, the ^{1}H NMR spectrum of **4** exhibited the signals for the methyl protons bonded to both Si atoms at δ 0.18, 0.16, 0.07, 0.05, as well as the *tert*-Bu protons at δ 0.94 and 0.87 in a 1:1 ratio. The ^{13}C NMR shows the signals corresponding to the methyl groups bonded to the Si atom at position 2 at δ –4.2 and –4.6, while those at δ –5.8 and –5.7 were assigned to the silyl ester at C-8 by comparison with the chemical shifts of **3**. Compound **4** having hydroxyl group could be of interest to get the olefin derivative and subsequent transformation to its dihydroxy derivative.

The 8-silylated derivative **3**, was transformed into 2-mesyloxy-8-*tert*-butyldimethylsilyloxyrosmarinecine (**5**) in 78 % yield by reaction with MsCl in pyridine, under N_2, at 0 °C for 72 h. The ^{1}H NMR data showed a singlet at δ 3.06 corresponding to the mesyl group, H-2 exhibited a doublet of doublet of triplets at δ 5.48, which is shielded 1.10 ppm to higher frequencies with respect to the same proton in **3**, confirming mesylation at C-2. Also compound **5** could be useful to get new hydroxypyrrolizidine alkaloids.

As in the previous case, the chemoselectivity of the protection at C-8 can be due to the absence of H-bonding in DMF (ε = 36.71). In order to obtain evidence for a solvent effect, the reaction between rosamarinecine **2** and *p*-toluensulfonylchlo-



Scheme 2. Reagents and conditions: (a) 1) KOH/MeOH/reflux, 2) Ac_2O/reflux, 3) $Ba(OH)_2/H_2O$/reflux, or direct hydrolysis of **1** with $Ba(OH)_2/H_2O$/reflux; (b) and (c) TDMSCl/DMF/Et_3N/DMAP/3h and /24h, respectively ; (d) MsCl/Py; (e) PTSCl/Py/0°C.

ride in pyridine was carried out giving 2-tosyloxyrosmarinecine (**6**). The results showed that the low reactivity of the OH groups at C-7 and C-8, could be explained by the presence of hydrogen bonds between these two hydroxyl groups in pyridine (ε = 12.30) which has a dielectric constant lower than DMF. The ^{1}H NMR spectrum shows the signals due to the tosyl methyl group at δ 2.40 and two doublets at δ 7.30 and 7.73 for the aromatic protons. Also, the ^{13}C NMR spectrum exhibits the aromatic carbons at δ 127.8, 129.9, 133.5, 145.0 and the methyl group at 21.7.

In conclusion, we describe the synthesis and characterization of pyrrolizidine alkaloids **3**, **4**, **5** and **6** obtained from selective protection of the different hydroxyl groups of rosmarinecine. The chemoselectivity of the silylation of the hydroxyl groups at positions C-2 and C-8 in **2** can be controlled by the time reaction as well as the different reactivity of the primary and secondary hydroxyl groups. Finally, these compounds could be good precursors of new polyhydroxylated pyrrolizidine alkaloids.

Acknowledgment

The authors thank Consejo Nacional de Ciencia y Tecnología (Conacyt) for financial support and a Ph.D scholarship to D.A.N.A to develop this work at Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, and Dr. Rosa Luisa Santillán for reading the manuscript and for her helpful comments.

Experimental

General

Reagents were purchased from Aldrich Co. The ^{1}H, ^{13}C NMR, ^{1}H-^{1}H COSY, HETCOR spectra were recorded on Jeol GLX-270, Jeol Eclipse-400 and Bruker Avance 300-DPX spectrometers. $CDCl_3$ and D_2O being used as solvent. The mass spectra were obtained with a Hewlett-Packard 59940-A mass spectrometer. The infrared spectra were recorded on a Perkin-Elmer 16F PC FT-IR spectrometer. Melting points were obtained with a Gallenkamp MFB-595 apparatus in open capillary and are uncorrected.

Extraction

Plant Material: *Senecio callosus* was collected in November 2001 in the State of Morelos (Voucher MEXU 521059, deposited in the Herbarium of the Instituto de Biología, UNAM). Extraction and Isolation: the general procedure has been described previously [11]. Rosmarinine (10 g) was obtained from air-dried root and aerial parts (1.5 Kg) and identified by spectroscopic data and comparison with an authentic sample.

Rosmarinecine (**2**): The reaction of 500 mg (1.41 mmol) of **1** and 700 mg of $Ba(OH)_2$ in 10 mL of H_2O was stirred under reflux for 3 h. After cooling to room temperature the solvent was evaporated under vacuum, 200 mL of acetonitrile were added to the residue and the mixture heating, after the solution was filtered and the filtrated was concentrated to yield 220 mg (90%) of **2**, mp 165-166 °C, lit [13] mp 169-170 °C. IR (KBr) ν (cm^{-1}): 3328, 2930, 1098, 1002. ^{1}H-NMR (400 MHz, D_2O), δ 2.10-2.19 (m, H-1), 4.17 (dt, *J* = 7.7, 9.4 Hz, H-2), 2.86 (dd, *J* = 8.1, 11.5 Hz, H-3$_a$), 2.08 (dd, *J* = 7.2, 11.5 Hz, H-3$_b$), 3.01 (ddd, *J* = 2.6, 7.5, 10.1 Hz, H-5$_a$), 2.55 (ddd, *J* = 7.5, 10.1, 11.5 Hz, H-5$_b$), 1.74-1.61 (m, H-6), 4.13-4.11 (m, H-7), 3.20 (dd, *J* = 2.9, 8.1 Hz, H-7$_a$), 3.81 (dd, *J* = 6.9, 11.4 Hz, H-8$_a$), 3.85 (dd, *J* = 4.5, 11.4 Hz, H-8$_b$).^{13}C-NMR (100 MHz, D_2O) δ 49.7 (C-1), 70.5 (C-2), 61.9 (C-3), 53.3 (C-5), 34.6 (C-6), 71.5 (C-7), 70.1 (C-7a), 58.8 (C-8). EI-MS: $[M]^+$ 173 (11 %), 155 (14 %), 129 (40 %), 112 (5%), 98 (100 %).

8-*tert*-butyl-dimethylsilyloxyrosmarinecine (**3**): The reaction under nitrogen atmosphere of 95 mg (0.549 mmol) of rosmarinecine **2** with 173 mg (1.15 mmol) of *tert*-butyl-dimethylsilane chloride (TDMSCl) in 2 mL of dimethylformamide, 0.8 mL of triethylamine, 0.01meq. of dimethylaminopyridine. The mixture was stirred at room temperature for 3 h and after the reaction was treated with 2 mL of a 0.1 N-NaOH solution, and then extractions with $CHCl_3$ were carried out. Sodium sulfate anhydrous was added to the organic phase and filtered; the solvent was eliminated under vacuum to yield 110 mg (70%) of **3**, mp 126-127° C. IR (KBr) ν(cm^{-1}): 3306, 2934,1260, 1080 and 944. ^{1}H-NMR (270 MHz, $CDCl_3$), δ 2.10-2.30 (m, H-1), 4.38 (dt, *J* = 8.5, 9.3 Hz, H-2), 2.85-3.05 (m, H-3), 3.13 (t, *J* = 9.3 Hz, H-5$_a$), 2.71 (dd, *J* = 3.8, 7.8 Hz, H-5$_b$), 1.60-1.90 (m, H-6), 4.07 (m, H-7), 3.23 (dd, J = 2.7, 11.8 Hz, H-7a), 4.00 (dd, *J* = 4.1, 11.8 Hz, H-8$_a$), 3.91 (dd, *J* = 2.1, 11.8 Hz, H-8$_b$), 0.13 (s, $SiCH_3$-9), 0.92 (s, $SiCCH_3$-11). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 50.7 (C-1), 69.2 (C-2), 64.7 (C-3), 54.1 (C-5), 31.1 (C-6), 71.7 (C-7), 72.6 (C-7a), 59.6 (C-8), -5.7 (Si-CH_3-9), 18.3 (Si-C-10), 25.9 (Si-C(C-11)$_3$). EI-MS: $[M]^+$ 287 (3 %), 269 (12 %), 230 (10%), 168 (17%), 138 (24 %), 98 (100%).

2,8-O-Disilyl*tert*butylrosmarinecine (**4**): The procedure to obtain **4** was the same used for **3**, a 84 mg (0.48 mmol) amount of compound **2** and 169 mg (1.13) of TDMSCl stirred for 24 h gave 136 mg (70%) of compound **4**, mp 138-140 °C. IR (KBr) ν (cm^{-1}): 3314, 2932, 1256, 1096, 1034, 842. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.40-2.55 (m, H-1), 4.72 (dt, *J* = 8.3, 9.1 Hz, H-2), 3.42 (dd, *J* = 8.3, 11.5 Hz, H-3$_a$), 3.05-3.25 (m, H-3$_b$, H-5$_b$), 3.85-4.05 (m, H-5a), 1.95-2.2 (m, H-6), 4.42 (m, H-7), 4.11 (dd, *J* = 4.1, 8.2 Hz, H-7a), 3.84-4.65 (m, H-8), 0.18 (s, $SiCH_3$-9), 0.16 (s, $SiCH_3$-9´), 0.94 (s, $SiCCH_3$-11), 0.07 (s, $SiCH_3$-12), 0.05 (s, $SiCH_3$-12´) and 0.87 (s, $SiCCH_3$-14). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 48.6 (C-1), 68.7 (C-2), 60.4 (C-3), 54.9 (C-5), 31.4 (C-6), 70.9 (C-7), 72.5 (C-7a),

57.6 (C-8), -5.8 (SiC-9), -5.7 ($SiCH_3$-9´), 18.0 (SiC-10), 25.9 (SiCC-11), -4.2 ($SiCH_3$-12), -4.6 ($SiCH_3$-12´), 18.3 (Si-C-13), 25.7 (SiCC-14). EI-MS: $[M]^+$ 401 (8%), 383 (50%), 212 (100%).

2-Mesyl-8-O-silyl*tert*butylrosmarinecine (**5**): The reaction of 40 mg (0.14 mmol) of compound **3** with 0.02 mL (0.03 mmol) of MsCl in 2 mL of pyridine was stirred for 72 h at 0 °C. After a NaOH-0.1N solution was added to the reaction mixture and then extractions with $CHCl_3$ were carried out. Sodium sulfate anhydrous was added to the organic phase and filtered; the solvent was eliminated under vacuum to yield 39 mg (78%) of **5**, as yellow oil. IR (net liquid) ν (cm^{-1}): 3326, 2954, 1380, 1250, 1100, 840. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.84-2.96 (m, H-1), 5.48 (dt, *J* = 6.0, 9.0 Hz, H-2), 3.90-4.10 (m, H-3_a, H-5_a, H-8), 3.60 (dd, *J* = 8.3, 12 Hz, H-3_b), 3.24 (td, *J* = 4, 4.7 Hz, H-5_b), 2.15-2.30 (m, H-6), 4.40-4.50 (m, H-7), 4.18 (dd, *J* = 4.0, 8.0 Hz, H-7a), 0.15 (s, $SiCH_3$-9). 0.95 (s, $SiCCH_3$-11) and 3.06 (s, OSO_2CH_3-12). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 46.5 (C-1), 73.9 (C-2), 60.6 (C-3), 54.9 (C-5), 32.1 (C-6), 71.0 (C-7), 73.6 (C-7a), 57.5 (C-8), -5.3 ($SiCH_3$-9), -5.4 ($SiCH_3$-9´), 18.6 (SiC-10), 26.2 ($SiCCH_3$-11) and 38.8 (OSO_2CH_3-12). EI-MS: $[M]^+$ 364 (2 %), 346 (5 %), 212 (62%), 153 (55%), 120 (38 %), 82 (100 %).

2-Tosylrosmarinecine (**6**): The reaction of 100 mg (0.578 mmol) of compound **2**, 450 mg (2.3 mmol) of PTSCl in 2 mL of pyridine under N_2 atmosphere at 0 °C was stirred for 72 h. After the reaction mixture was treated with a NH_4OH-5N solution to get a pH = 11 and then extractions with $CHCl_3$ were carried out. Sodium sulfate anhydrous was added to the organic phase and filtered; the solvent was eliminated under vacuum to yield 170 mg (95%) of compound **6** as yellow oil. IR (net liquid) ν (cm^{-1}): 3340, 3030, 2940, 2710, 1600, 1410, 1100. ^{1}H-NMR (270 MHz, $CDCl_3$), δ 2.75-2.84 (m, H-1), 4.66 (dt, *J* = 5, 12 Hz, H-2), 2.85-3.05 (m, H-3), 2.95-3.05 (dd, *J* = 8.3, 12 Hz, H-5_a), 2.46 (ddd, *J* = 3.3, 5.9, 9.3 Hz, H-5_b), 1.95 (m, H-6_a), 1.65-1.80 (m, H-6_b), 4.14 (t, *J* = 4.1, Hz, H-7), 4.01 (dd, *J* = 4.1, 7.7 Hz, H-7a), 3.72 (dd, *J* = 2.1, 9.5 Hz, H-8_a), 3.58 (dd, *J* = 5.8, 9.5 Hz, H-8_b), 7.30 (d, *J* = 8.1, Hz, H-10), 7.73 (d, *J* = 8.1, Hz, H-11), 2.40 (s, H-13). ^{13}C-NMR (75 MHz, $CDCl_3$) d 51.9 (C-1), 85.1 (C-2), 58.6 (C-3), 53.0 (C-5), 32.2 (C-6), 84.4 (C-7), 73.7 (C-7a), 72.4 (C-8), 145.0 (C-9), 129.9 (C-10), 127.8 (C-11), 133.5 (C-12), 21.7 (C-13). EI-MS: $[M]^+$ 310 (16 %), 154 (85 %), 137 (100 %).

2,7,8-Triacetylrosmarinecine (**7**): The reaction of 400 mg (1.13 mmol) of **1**, 700 mg of KOH in 15 mL of methanol was stirred and under reflux by 2 h. After cooling to room temperature the solvent was eliminated and 10 mL of acetic anhydride were added to the residue. The mixture was stirred and kept under reflux for 0.5 h. After being cooled to room temperature, and H_2SO_4 (2.5%) was added slowly, the solution was treated with hexane and the mixture was treated with NH_4OH-5N to get pH = 11, then extractions with $CHCl_3$ were carried out and the solvent was eliminated under vacuum to yield 289 mg (85%) of 7 as a solid, mp 115-6 °C, lit [12] mp 138-9 °C (characterized as its picrate). ^{1}H-NMR (400 MHz, $CDCl_3$), δ 2.72-2.81 (m, H-1), 4.98-5.10 (m, H-2), 3.17 (dd, *J* = 8, 11.4 Hz, H-3a), 3.01 (dd, *J* = 8, 11.4 Hz, H-3b), 3.2-3.3 (m, H-5a), 2.71 (m, H-5b), 1.90-2.10 (m, H-6), 4.98-5.10 (m, H-7), 3.57 (d, *J* = 3.8 Hz, H-7a), 4.32 (dd, *J* = 7.3, 10 Hz, H-8a), 4.13 (dd, *J* = 9, 10 Hz, H-8b), 2.06 (s, H-11), 2.04 (s, H-14), 2.10 (s, H-17). ^{13}C-NMR (400 MHz, $CDCl_3$) δ 44.6 (C-1), 75.4 (C-2), 61.3 (C-3), 53.3 (C-5), 34.0 (C-6), 75.1 (C-7), 68.0 (C-7a), 62.6 (C-8), 21.6 (C-11), 20.7 (C-14), 20.6 (C-17), 169.78, 170.72, 170.73 (CO groups). EI-MS: $[M]^+$ = 300 (15%), 239 (25%), 179 (21%), 153 (21%), 136 (41%), 119 (75%), 93 (62%), 80 (42%), 43 (100%).

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