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# Michael-Type Amine Adducts of α-Methylene-γ-Lactones tomentosin

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## Abstract

In the present study, novel amino lactone derivatives of tomentosin **2** were efficiently prepared through a diastereoselective conjugate addition of several secondary amines to the α-methylene-γ-butyrolactone function of tomentosin **1**, a sesquiterpene lactone extracted from *Dittrichia viscosa*. These compounds were fully characterized by spectroscopic methods.

***Keywords:*** *Tomentosin; Dittrichia Viscosa;Michael addition, Amino-tomentosin.*

## 1. Introduction

Plants have a long history as therapeutics in the treatment of human diseases and have been a continuous source of inspiration for the development of new medicines. Numerous compounds of interest have been isolated and identified from these plants such as flavonoids, monoterpenes, triterpenoids, and polyphenols. This genus is also a rich source of sesquiterpene lactones. Many studies have focused on sesquiterpene lactones since they exhibit a wide range of biological properties [1,2] (Fig. 1). They can also serve as starting material for the synthesis of more complex bioactive compounds [3]. Dittrichia viscosa (L.) W. Greuter [4,5] is a tough plant that is widespread in the Mediterranean region. This plant is used either as extracts or essential oil in traditional Moroccan medicine for its antipyretic, antiseptic and anti-inflammatory properties [6,7]. Considered as an invasive species and particularly abundant in wasteland areas, this perennial plant proved to be a rich source of natural products and it could accordingly be used as a renewable source of sesquiterpene lactones such as tomentosin, santonin, helenin and tayunin [8-11]. Therefore, we exploited herein the highly electrophilic $\alpha$-methylene-$\gamma$-lactone ring naturally present in the tomentosin to form a libraries of structurally original amino-lactone derivatives of tomentosin via Michael addition reaction.

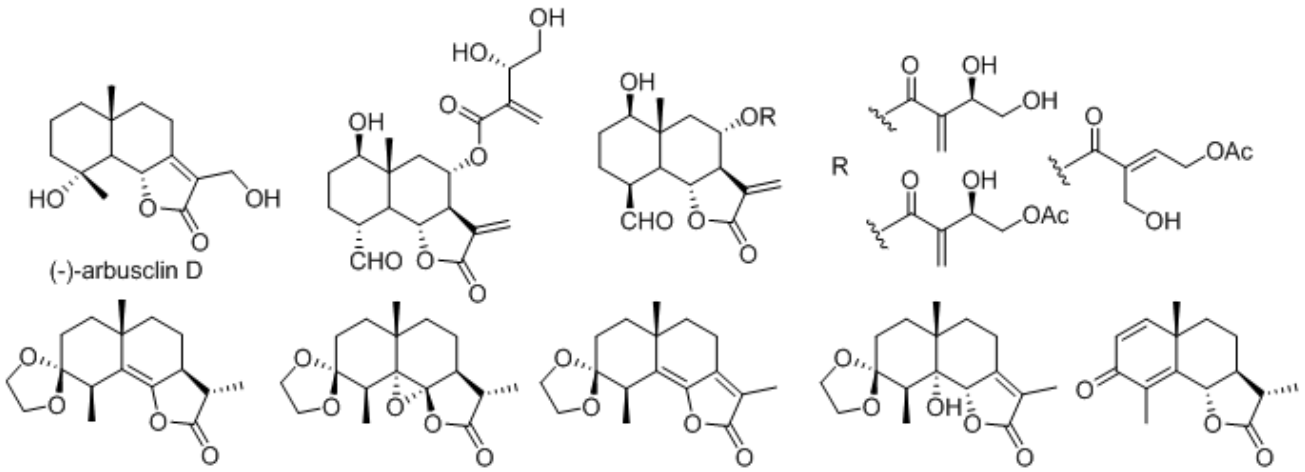



**Figure 1.** Examples of biologically active sesquiterpene lactones.

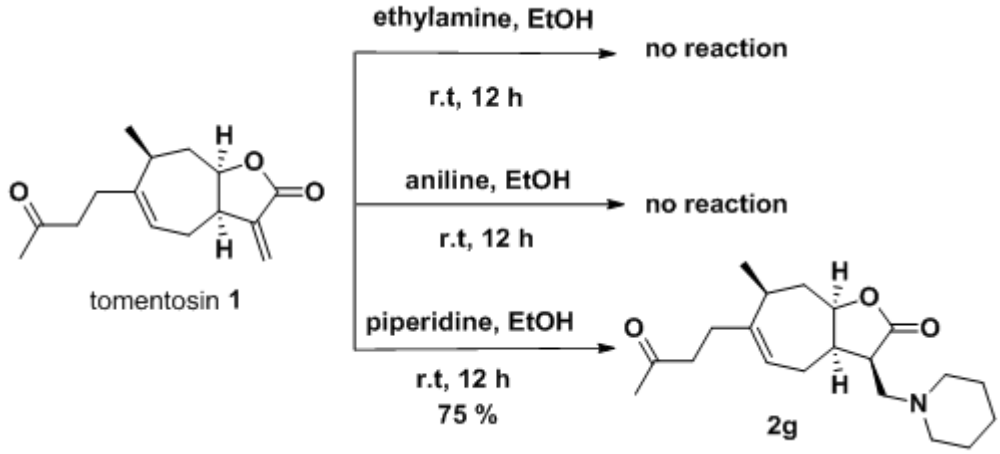
## 2. Materials and methods

All reagents were purchased from commercial suppliers and were used without further purification. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation. Flash column chromatography was performed on silica gel 60 (230-400 mesh, 0.040-0.063 mm). $^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker avance 400.13 ($^{13}$C, 101MHz), or on a Bruker advance III HD nanobay 400.13 ($^{13}$C, 101 MHz). Chemical shifts are given in parts per million from tetramethylsilane (TMS) as internal standard. The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiple. Coupling constants (*J*) are reported in hertz (Hz). Multiplicities were determined by the DEPT 135 sequence. High resolution mass spectra (HRMS (ESI)) were performed on a Maxis Bruker 4G by the "Federation de Recherche" ICOA/CBM (FR2708) platform.

## 3. Results and Discussions

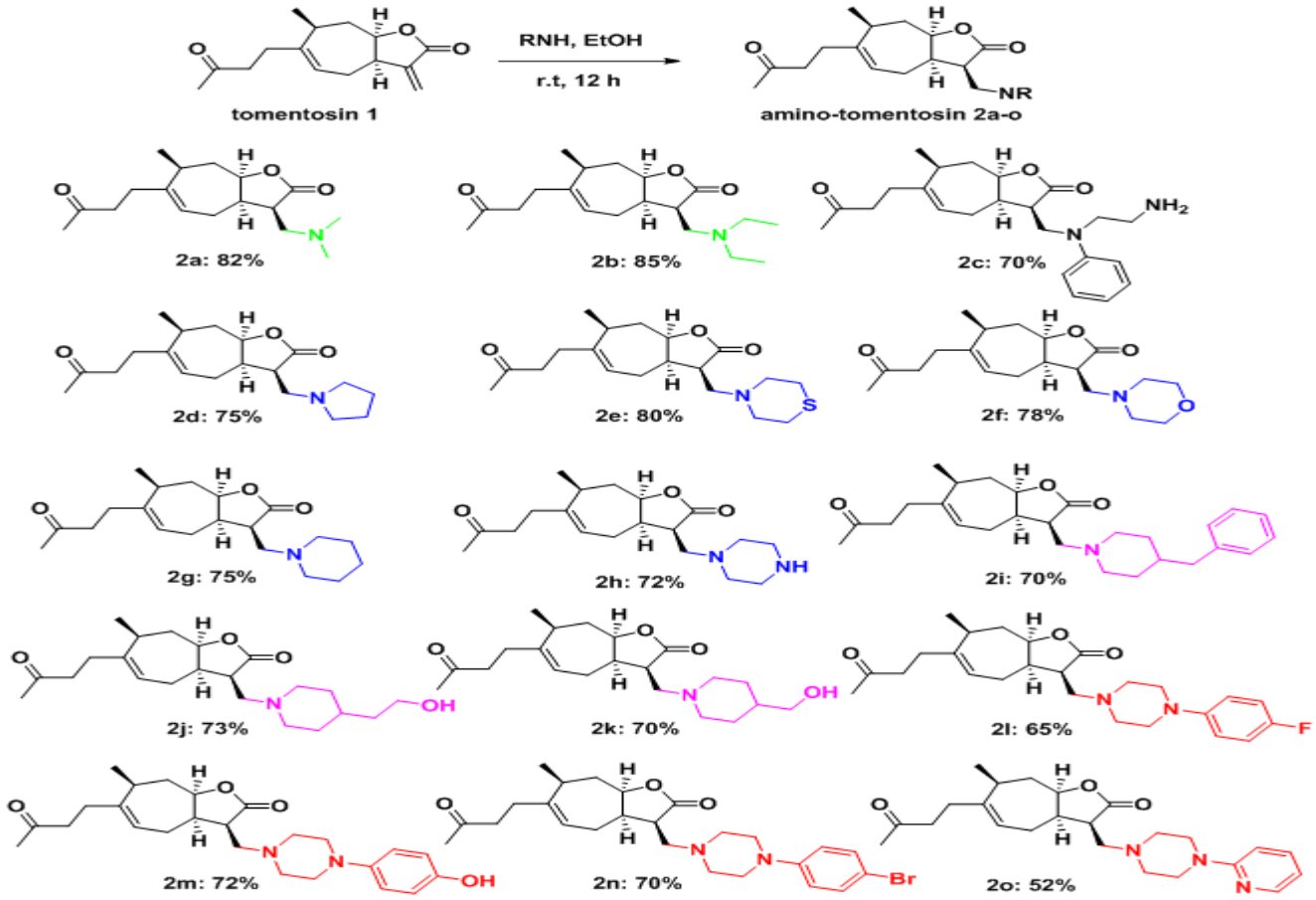
The reaction of tomentosin **1** with a variety of amines was performed in ethanol at room temperature for 12 h [12] (Fig. 2). Only starting material was recovered in the case of the primary and aromatic amine. However, under the same

conditions, tomentosin-piperidine **2g** was isolated with 75 % yield. These results can be explained by the difference in nucleophilicity which is more important in secondary amines compared to primary and aromatic amines.




**Scheme.1** Reactivity of tomentosin with different amines

To generalize this reaction, various secondary amines were then used to generate a library of amino-tomentosin analogues using the optimized reaction conditions (Scheme 2). The reactions were clean and the expected products were synthesized in good yields. The amino-tomentosin **2a-o** were obtained as one diastereomer after purification by flash chromatography. The operating conditions are compatible with the introduction of non-cyclic aliphatic amines such as dimethylamine and diethylamine (**2a** and **2b**) and aliphatic cyclic amines such as pyrrolidine, thiomorpholine, morpholine, piperidine and piperazine, the desired products were isolated with good yield (**2d-h**). The use of *N*-phenylethylenediamine containing both a primary and secondary amine was carried out successfully, the product **2c** was isolated with 70% yield; only the secondary amine was reacted, which confirms the result obtained in the optimization step. The methodology was also extended to piperidine substituted in the position 4 by a benzyl **2i**, alcohols **2j-k**, as well as piperazine substituted in the position 4 by phenyl bearing different groups (F, OH, Br) **2l-n** and pyridine **2o**. The structures of the amino-tomentosin were confirmed by their $^{1}H$, $^{13}C$ and 2D NMR spectroscopic data as described for **2j**. The $^{1}H$ NMR spectra showed the disappearance of the alkene protons of tomentosin at 5,4 and 6,18 ppm. While $^{13}C$ NMR confirms the disappearance of two signals corresponding respectively to carbons C-11 at 139.2 ppm and C-13 at 122.3 ppm. A Nuclear Overhauser Effect Spectroscopy (NOESY)-NMR experiment allowed us to determine the configuration R for new asymmetric center C-11. This experiment shows the correlation of H-11 with H-8 (Fig 2).




**Scheme.2** Synthesis of amino-tomentosin

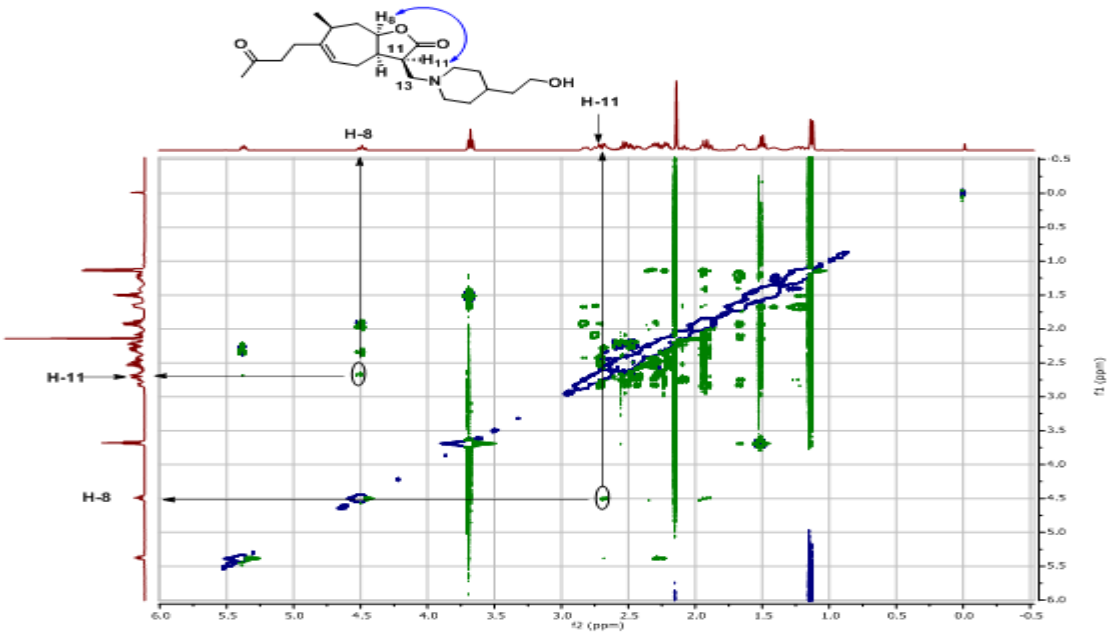



**Figure 2** $^{1}$H, $^{1}$H–COSY correlations of **2j**.

***Experimental data***

**(11*R*)-13-dimethylamino-11,13-dihydrotomentosin (2a)**

RMN $^{1}$H (400 MHz, $CDCl_3$) : $\delta$ 5.29 (dd, $J$ = 8.9, 5.5 Hz, 1H), 4.47 – 4.39 (m, 1H), 2.61 – 2.14 (m, 11H), 2.14 – 2.12 (m, 6H), 2.05 (s, 3H), 1.90 – 1.78 (m, 2H), 1.05 (d, $J$ = 6.9 Hz, 3H) ppm. RMN $^{13}$C (101 MHz, $CDCl_3$) : $\delta$ 208.2, 178.1, 144.1, 120.6, 79.7, 59.7, 45.9, 43.6, 42.7, 42.5, 35.9, 35.4, 30.4, 30.0, 27.0, 20.8 ppm. HRMS (ESI+): calcd For $C_{17}H_{28}NO_3$ $[M+H]^+$ 294.2062; found 294.2063.

**(11*R*)-13-diethylamino-11,13-dihydrotomentosin (2b)**

RMN $^{1}$H (400 MHz, $CDCl_3$) : $\delta$ 5.38 – 5.31 (m, 1H), 4.48 (ddd, $J$ = 10.7, 8.5, 3.9 Hz, 1H), 2.77 – 2.15 (m, 15H), 2.11 (s, 3H), 1.98 – 1.84 (m, 2H), 1.11 (d, $J$ = 6.9 Hz, 3H), 0.96 (t, $J$ = 7.1 Hz, 6H) ppm. RMN $^{13}$C (101 MHz, $CDCl_3$) : $\delta$ 208.4, 178.7, 144.2, 120.9, 79.9, 54.0, 47.2, 44.0, 43.1, 42.9, 36.1, 35.7, 30.6, 30.2, 27.4, 21.0, 11.9 ppm. HRMS (ESI+): calcd For $C_{19}H_{32}NO_3$ $[M+H]^+$ 322.2374; found 322.2376.

**(11*R*)-13-(*N*-phenylethylenediamine)-11,13-dihydrotomentosin (2c)**

RMN $^{1}$H (400 MHz, $CDCl_3$) : $\delta$ 7.16 – 7.07 (m, 2H), 6.68 – 6.52 (m, 3H), 5.39 – 5.23 (m, 1H), 4.44 (ddd, $J$ = 11.7, 8.6, 3.1 Hz, 1H), 4.33 – 3.80 (m, 1H), 3.13 (dd, $J$ = 6.6, 4.9 Hz, 2H), 2.89 – 2.72 (m, 4H), 2.67 – 2.12 (m, 8H), 2.09 (s, 3H), 2.07 – 1.78 (m, 2H), 1.09 (d, $J$ = 6.9 Hz, 3H) ppm. RMN $^{13}$C (101 MHz, $CDCl_3$) : $\delta$ 208.1, 178.3, 148.5, 144.4, 129.2, 119.9, 117.3, 113.0, 79.7, 48.6, 48.2, 45.0, 43.3, 42.7, 40.9, 35.6, 35.5, 30.4, 30.0, 26.6, 20.7 ppm. HRMS (ESI+): calcd For $C_{23}H_{33}N_2O_3$ $[M+H]^+$ 385.2484; found 385.2485.

**(11*R*)-13-pyrrolidine-11,13-dihydrotomentosin (2d)**

RMN $^{1}$H (400 MHz, $CDCl_3$) : $\delta$ 5.35 (dd, $J$ = 8.9, 5.5 Hz, 1H), 4.49 (ddd, $J$ = 11.8, 8.6, 3.6 Hz, 1H), 2.73 (tt, $J$ = 8.9, 3.7 Hz, 2H), 2.58 – 2.14 (m, 13H), 2.12 (s, 3H), 1.98 – 1.86 (m, 2H), 1.77 – 1.67 (m, 4H), 1.11 (d, $J$ = 6.9 Hz, 3H) ppm. RMN $^{13}$C (101 MHz, $CDCl_3$) : $\delta$ 208.4, 178.4, 144.2, 120.8, 79.9, 56.0, 54.7, 44.8, 42.9, 42.5, 36.1, 35.7, 30.6, 30.2, 27.2, 23.9, 21.0 ppm. HRMS (ESI+): calcd For $C_{19}H_{30}NO_3$ $[M+H]^+$ 320.2217; found 320.2220.

**(11*R*)-13-thiomorpholine-11,13-dihydrotomentosin (2e)**

RMN $^{1}$H (400 MHz, $CDCl_3$) : $\delta$ 5.34 (ddt, $J$ = 8.4, 5.5, 1.4 Hz, 1H), 4.47 (ddd, $J$ = 11.6, 8.5, 2.9 Hz, 1H), 2.79 – 2.15 (m, 19H), 2.12 (s, 3H), 1.98 – 1.80 (m, 2H), 1.11 (d, $J$ = 6.9 Hz, 3H) ppm. RMN $^{13}$C (101 MHz, $CDCl_3$) : $\delta$ 208.3, 178.2, 144.5, 120.4, 79.8, 59.1, 55.7, 43.1, 42.9, 42.8, 35.9, 35.7, 30.5, 30.2, 28.1, 27.1, 20.9 ppm. HRMS (ESI+): calcd For $C_{19}H_{30}NO_3S$ $[M+H]^+$ 352.1938; found 352.1940.

**(11*R*)-13-morpholine-11,13-dihydrotomentosin (2f)**

RMN $^{1}$H (400 MHz, $CDCl_3$) : $\delta$ 5.37 – 5.31 (m, 1H), 4.47 (ddd, $J$ = 11.6, 8.6, 2.9 Hz, 1H), 3.70 – 3.58 (m, 4H), 2.68 (td, $J$ = 12.7, 6.0 Hz, 2H), 2.58 – 2.15 (m, 13H), 2.11 (s, 3H), 1.97 – 1.81 (m, 2H), 1.10 (d, $J$ = 6.9 Hz, 3H) ppm. RMN $^{13}$C (101 MHz, $CDCl_3$) : $\delta$ 208.3, 178.2, 144.4, 120.4, 79.8, 67.1, 58.9, 54.2, 42.8, 42.8, 42.8, 35.9, 35.7, 30.5, 30.1, 27.1, 20.9 ppm. HRMS (ESI+): calcd For $C_{19}H_{30}NO_4$ $[M+H]^+$ 336.2169; found 336.2169.

**(11*R*)-13-piperidine-11,13-dihydrotomentosin (2g)**

RMN $^{1}$H (400 MHz, $CDCl_3$) : $\delta$ 5.38 (t, $J$ = 7.2 Hz, 1H), 4.49 (ddd, $J$ = 11.6, 8.6, 3.2 Hz, 1H), 2.72 – 2.61 (m, 2H), 2.61 – 2.17 (m, 13H), 2.14 (s, 3H), 2.00 – 1.84 (m, 2H), 1.53 (td, $J$ = 6.3, 4.1 Hz, 4H), 1.42 (q, $J$ = 5.7 Hz, 2H), 1.13 (d, $J$ = 6.9 Hz, 3H) ppm. RMN $^{13}$C (101 MHz, $CDCl_3$) : $\delta$ 208.4, 178.7, 144.3, 120.9, 79.9, 59.5, 55.2, 43.2, 43.0, 43.0,

36.1, 35.8, 30.6, 30.2, 27.2, 26.3, 24.6, 21.0 ppm. HRMS (ESI+): calcd For $C_{20}H_{32}NO_3$ $[M+H]^+$ 334.2373; found 334.2376.

**(11*R*)-13-piperazine-11,13-dihydrotomentosin (2h)**

RMN $^1H$ (400 MHz, $CDCl_3$) : $\delta$ 5.37 (dd, $J$ = 8.3, 5.9 Hz, 1H), 4.50 (ddd, $J$ = 11.6, 8.6, 2.9 Hz, 1H), 2.91 – 2.18 (m, 19H), 2.14 (s, 3H), 2.00 – 1.83 (m, 2H), 1.24 (s, 1H), 1.13 (d, $J$ = 6.9 Hz, 3H) ppm. RMN $^{13}C$ (101 MHz, $CDCl_3$) : $\delta$ 208.4, 178.5, 144.4, 120.6, 79.9, 59.3, 55.2, 46.3, 43.0, 43.0, 42.9, 36.1, 35.8, 30.6, 30.2, 27.2, 21.0 ppm. HRMS (ESI+): calcd For $C_{19}H_{31}N_2O_3$ $[M+H]^+$ 335.2327; found 335.2329.

**(11*R*)-13-(4-benzylpiperidine)-11,13-dihydrotomentosin (2i)**

RMN $^1H$ (250 MHz, $CDCl_3$) : $\delta$ 7.32 – 7.09 (m, 5H), 5.39 (t, $J$ = 7.2 Hz, 1H), 4.49 (ddd, $J$ = 10.8, 8.4, 3.8 Hz, 1H), 2.86 – 2.18 (m, 15H), 2.15 (s, 3H), 2.11 – 1.79 (m, 4H), 1.60 (dt, $J$ = 12.6, 2.5 Hz, 2H), 1.50 (dt, $J$ = 7.3, 3.6 Hz, 1H), 1.28 (qd, $J$ = 10.9, 9.5, 4.6 Hz, 2H), 1.14 (d, $J$ = 6.8 Hz, 3H) ppm. RMN $^{13}C$ (63 MHz, $CDCl_3$) : $\delta$ 208.4, 178.6, 144.3, 140.9, 129.4, 128.4, 126.1, 120.8, 79.9, 59.0, 55.7, 53.2, 43.5, 43.1, 43.1, 43.0, 38.1, 36.1, 35.7, 32.7, 32.3, 30.6, 30.2, 27.2, 21.0 ppm. HRMS (ESI+): calcd For $C_{27}H_{38}NO_3$ $[M+H]^+$ 424.2841; found 424.2846.

**(11*R*)-13-(4-piperidinethanol)-11,13-dihydrotomentosin (2j)**

RMN $^1H$ (400 MHz, $CDCl_3$) : $\delta$ 5.37 – 5.30 (m, 1H), 4.46 (ddd, $J$ = 11.7, 8.5, 3.3 Hz, 1H), 3.63 (t, $J$ = 6.6 Hz, 2H), 2.82 – 2.14 (m, 14H), 2.11 (s, 3H), 2.04 (td, $J$ = 11.6, 2.6 Hz, 2H), 1.96 – 1.80 (m, 4H), 1.62 – 1.12 (m, 5H), 1.10 (d, $J$ = 6.9 Hz, 3H) ppm. RMN $^{13}C$ (101 MHz, $CDCl_3$) : $\delta$ 208.5, 178.6, 144.2, 120.7, 79.8, 60.6, 59.0, 55.6, 53.2, 43.0, 43.0, 42.9, 39.6, 36.0, 35.7, 32.7, 32.5, 32.4, 30.5, 30.1, 27.1, 20.9 ppm. HRMS (ESI+): calcd For $C_{22}H_{36}NO_4$ $[M+H]^+$ 378.2635; found 378.2638.

**(11*R*)-13-(4-piperidinemethanol)-11,13-dihydrotomentosin (2k)**

RMN $^1H$ (400 MHz, $CDCl_3$) : $\delta$ 5.36 – 5.30 (m, 1H), 4.45 (ddd, $J$ = 11.8, 8.6, 3.5 Hz, 1H), 3.42 (d, $J$ = 6.3 Hz, 2H), 2.85 – 2.70 (m, 2H), 2.69 – 2.13 (m, 13H), 2.10 (s, 3H), 2.04 (td, $J$ = 11.5, 2.6 Hz, 1H), 1.95 – 1.80 (m, 3H), 1.70 – 1.59 (m, 2H), 1.43 (dqd, $J$ = 12.0, 6.9, 3.0 Hz, 1H), 1.19 (dtd, $J$ = 21.6, 12.8, 12.4, 3.9 Hz, 2H), 1.09 (d, $J$ = 6.9 Hz, 3H) ppm. RMN $^{13}C$ (101 MHz, $CDCl_3$) : $\delta$ 208.5, 178.6, 144.1, 120.6, 79.8, 67.7, 58.8, 55.1, 52.8, 43.0, 42.8, 42.8, 38.6, 35.9, 35.5, 30.4, 30.1, 29.1, 28.8, 26.9, 20.8 ppm. HRMS (ESI+): calcd For $C_{21}H_{34}NO_4$ $[M+H]^+$ 364.2480; found 364.2482.

**(11*R*)-13-(4-fluorophenylpiperazine)-11,13-dihydrotomentosin (2l)**

RMN $^1H$ (400 MHz, $CDCl_3$) : $\delta$ 6.95 – 6.88 (m, 2H), 6.86 – 6.79 (m, 2H), 5.34 (dd, $J$ = 8.5, 5.8 Hz, 1H), 4.49 (ddd, $J$ = 11.6, 8.6, 3.1 Hz, 1H), 3.12 – 3.01 (m, 4H), 2.81 – 2.15 (m, 15H), 2.11 (s, 3H), 1.98 – 1.82 (m, 2H), 1.11 (d, $J$ = 6.9 Hz, 3H) ppm. RMN $^{13}C$ (101 MHz, $CDCl_3$) : $\delta$ 208.3, 178.2, 157.3, 148.1, 144.4, 120.4, 118.0, 117.9, 115.8, 115.5, 79.8, 58.4, 53.7, 50.3, 42.9, 42.9, 42.8, 35.9, 35.6, 30.5, 30.1, 27.1, 20.9 ppm. HRMS (ESI+): calcd For $C_{25}H_{34}FN_2O_3$ $[M+H]^+$ 429.2541; found 429.2547.

**(11*R*)-13-(4-hydroxyphenylpiperazine)-11,13-dihydrotomentosin (2m)**

RMN $^1H$ (400 MHz, $CDCl_3$) : $\delta$ 6.81 – 6.66 (m, 4H), 5.34 – 5.23 (m, 1H), 4.48 (ddd, $J$ = 11.7, 8.5, 3.2 Hz, 1H), 3.07 – 2.93 (m, 4H), 2.75- 2.23 (m, 16H), 2.11 (s, 3H), 1.96 – 1.79 (m, 2H), 1.09 (d, $J$ = 6.8 Hz, 3H) ppm. RMN $^{13}C$ (101

MHz, $CDCl_3$) : $\delta$ 209.2, 178.6, 150.7, 145.0, 144.2, 120.4, 118.7, 116.1, 80.0, 58.2, 53.6, 50.9, 42.9, 42.8, 42.7, 35.8, 35.5, 30.4, 30.1, 26.9, 20.8 ppm. HRMS (ESI+): calcd For $C_{25}H_{35}N_2O_4$ $[M+H]^+$ 427.2586; found 427.2591.

**(11*R*)-13-(4-bromophenylpiperazine)-11,13-dihydrotomentosin (2n)**

RMN $^1H$ (250 MHz, $CDCl_3$) : $\delta$ 7.37 – 7.27 (m, 2H), 6.80 – 6.70 (m, 2H), 5.41 – 5.30 (m, 1H), 4.51 (ddd, *J* = 10.9, 8.5, 3.6 Hz, 1H), 3.12 (ddd, *J* = 6.0, 4.2, 2.2 Hz, 4H), 2.84 – 2.16 (m, 15H), 2.13 (s, 3H), 2.04 – 1.80 (m, 2H), 1.13 (d, *J* = 6.9 Hz, 3H) ppm. RMN $^{13}C$ (63 MHz, $CDCl_3$) : $\delta$ 208.3, 178.2, 150.5, 144.5, 132.1, 120.4, 117.8, 112.0, 79.9, 58.4, 53.6, 49.2, 43.0, 42.9, 42.9, 36.0, 35.7, 30.6, 30.2, 27.1, 20.9 ppm. HRMS (ESI+): calcd For $C_{25}H_{34}BrN_2O_3$ $[M+H]^+$ 489.1740; found 489.1747.

**(11*R*)-13-(2-pyridylpiperazine)-11,13-dihydrotomentosin (2o)**

RMN $^1H$ (400 MHz, $CDCl_3$) : $\delta$ 8.13 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 6.62 – 6.54 (m, 2H), 5.37 – 5.25 (m, 1H), 4.49 (ddd, *J* = 11.6, 8.5, 3.2 Hz, 1H), 3.48 (tdt, *J* = 15.9, 10.1, 3.4 Hz, 4H), 2.78- 2.13 (m, 15H) , 2.10 (s, 3H), 1.97 – 1.83 (m, 2H), 1.10 (d, *J* = 6.9 Hz, 3H) ppm. RMN $^{13}C$ (101 MHz, $CDCl_3$) : $\delta$ 208.3, 178.2, 159.7, 148.1, 144.4, 137.6, 120.4, 113.6, 107.3, 79.8, 58.6, 53.5, 45.4, 42.9, 42.9, 42.8, 35.9, 35.6, 30.5, 30.1, 27.1, 20.9 ppm. HRMS (ESI+): calcd For $C_{24}H_{34}N_3O_3$ $[M+H]^+$ 412.2589; found 412.2594.

## 4. Conclusion

In summary, we described here the synthesis of interesting amino-lactone derivatives of tomentosin by a Michael addition reaction of various secondary amines to the natural compound. We used an enantiomerically pure and natural starting material, there by limiting the chemical impact on the environment. This procedure allowed us to generate enantiomerically pure amino compounds in one diastereoisomer form with a limited number of steps.

## References


[1] M. Ando, K. Isogai, H. Azami, N. Hirata, H.Yamasaki, Y. Yanagi, *J. Nat. Prod.*, 55 (1992) 1620-1625.

[2] A. C. Cao, X. C. Zhang, M. X. Guo, M. Wang, L. Shi, Y. Q. Tu, *Chin. J. Pestic.*, 44 (2005) 37.

[3] M. E. Maier, *Org. Biomol. Chem*., 13 (2015) 5302-5343.

[4] I. Chiappini, G. Fardella, A. Mengini, C. Rossi, *Planta Med*., 44 (1982) 159-161.

[5] Flora Europea; T. G. Tutin, V. H. Heywood, N. A. Burges, D. M. Moore, S. H. Valentine, S. M. Walters, D. A. Webb, Eds.; Cambridge University: London, UK, 1976; Vol. 4.

[6] N.-A. Zeggwagh, M. -L. Ouahidi, A. Lemhadri, M. Eddouks, *J. Ethnopharmacol*., 108 (2006) 223-227.

[7] P. Barbetti, I. Chiappini, G. Fardella, A. Menghini, *Planta Med*., 51 (1985) 471.

[8] F. Bohlmann, P. K. Mahanta, J. Jakupovic, R. C. Rastogi, A. A. Natu, *Phytochemistry.*, 17 (1978) 1165-1172.

[9] C. Willuhn, A. Skibinski, T. J. Schmidt, *Planta Med*., 64 (1998) 635-639.

[10] P. Azoulay, J. P. Reynier, G. Balansard, M. Gasquet, *Pharm. Acta Helv*., 61 (1986) 345-352.

[11] M. Maoz, Y. Kashman, I. Neeman, *Planta Medica*., 65 (1999) 281-282.

[12] M. Moumou, A. El Bouakher, H. Allouchi, A. El Hakmaoui, A. Benharref, V. Mathieu, G. Guillaumet, M. Akssira, *Bioorg. Med. Chem. Lett*., 24 (2014) 4014-4018.