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Novel erythromycin A 9-tritylhydrazone: selective 6-O-methylation and conformational analysis

Ernesto Brunet [a,*], Francisco Parra [a], Susana Mantecón [a], Olga Juanes [a,b], Juan Carlos Rodríguez-Ubis [a], M[a] Carmen Cruzado [b], Ramón Asensio [b]

[a] *Departamento de Química Orgánica, Universidad Autónoma de Madrid, 28049 Madrid, Spain*
[b] *Ercros-Farmacia S.A. Paseo del Deleite s/n, Aranjuez, 28300 Madrid, Spain*

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Abstract

The straightforward synthesis of the novel 9-tritylhydrazone erythromycin A and its highly regioselective O-methylation at C(6)–OH are described. Preliminary conformational data based on X-ray diffraction, ^{1}H NMR and molecular mechanics is also presented with the aim of understanding the observed high regioselectivity. The facile synthesis of 6,12-*O*-dimethylerythromycin A, a standard to assess clarithromycin purity in quality control processes, is reported as well.

Keywords: Erythromycin; Clarithromycin; Regioselective methylation; Conformational analysis

Clarithromycin (Fig. 1) is an important member of the family of the 14-membered macrolide antibiotics which are active in vitro against clinically important gram-positive and gram-negative bacteria.[1]

Clarithromycin was derived from erythromycin A by regioselective methylation at 6-OH position. There are a myriad of methods to perform this regioselective alkylation.[2] The most important ones involve direct blocking of the highly reactive hydroxy groups at 2′ and 4″ positions and indirect protection of the hydroxyl groups at 11 and 12 positions by placing relatively bulky groups at position 9, by means of the reversible, appropriate transformation of the ketone group.

We hereby report the synthesis of the novel erythromycin A 9-tritylhydrazone **3** (Fig. 2) and the excellent results concerning the 6-O-methylation of its 2′,4″-*O*-bistrimethylsilyl derivative.[3]

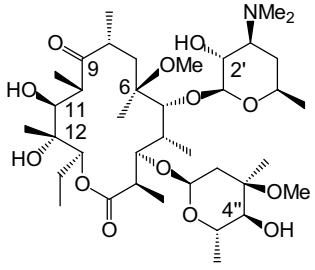

Fig. 1. Structure of clarithromycin **1**.

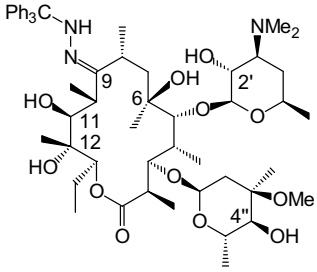

Fig. 2. Structure of the novel erythromycin A 9-tritylhydrazone **3**.

* Corresponding author. Tel.: +34 914973926; fax: +34 914973966.
E-mail address: ernesto.brunet@uam.es (E. Brunet).

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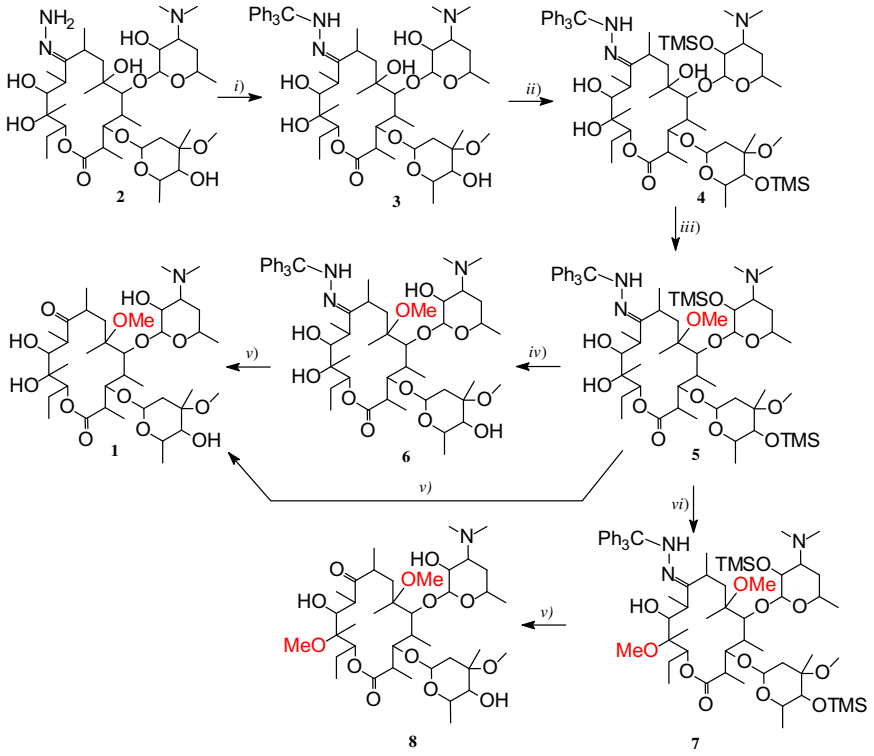

Scheme 1. Reagents and conditions: (i) $Ph_3CCl/Et_3N/CH_2Cl_2$ rt 1 h, 99%; (ii) TMS-imidazole/TMSCl/CH_2Cl_2, 0 °C, 2 h, 98%; (iii) KOH/MeI/THF–DMSO (1:1) see text, 80%; (iv) HCO_2H/EtOH/H_2O, 97%; (v) $NaNO_2/HCO_2H/CH_3CN/H_2O$ 0 °C, 73%; (vi) NaH/MeI/THF–DMSO (1:1) 0 °C, 16 h, 44%.

Scheme 1 outlines the overall process (stereochemistry has been omitted but is identical to that of Figures 1 and 2). The starting material, erythromycin A hydrazone **2**,[4] was easily transformed into the triphenylmethyl (trityl) derivative in high isolated yields by the reaction with triphenylchloromethane.[5] The corresponding erythromycin A 9-tritylhydrazone **3** was quantitatively silylated at 2′ and 4″ positions using standard conditions.[6] The key regioselective step was carried out on the 2′,4″-*O*-bistrimethylsilyl-erythromycin A 9-tritylhydrazone **4**.

The best results in the methylation of the latter were attained in a 1:1 THF–DMSO mixture at 0 °C by addition of up to 6 equiv of methyl iodide first, followed by up to 4 equiv of ground potassium hydroxide.[7] Interestingly, no further methylation at 11- and/ or 12-OH positions was observed in these conditions, despite the use of those large excesses of MeI and KOH. This is in strong contrast to what happened in our previous work concerning the corresponding 9-*O*-(2-pyrimidyl)oxime homolog[8] and in other oxime ketal derivatives,[9] where the 6,11-*O*-dimethyl compounds were easily produced in relatively high amounts, thus compromising the purity and chemical yield of the final clarithromycin. Larger amounts of MeI/KOH allowed us to detect very small amounts of the 6,12-*O*-dimethyl (yet no 6,11-*O*-dimethyl) which suggests that the bulky trityl group effectively hampers the reaction of the hydroxyl groups at 12 and, especially, 11 position, the latter being fairly reactive in other ketone-protected erythromicine A derivatives. Unfortunately, we were unable to get good crystals from compound **4** but Figure 3 shows instead the single-crystal X-ray diffraction results from compound **3**.[10]

From the visual inspection of this structure one cannot easily explain the observed differential reactivity of the three OH groups on exclusively steric grounds because the OH group on position 6 appears to be precisely the most hindered one. Besides, the X-ray data of compound **3** indicate that the oxygen atom of 6-OH establishes a hydrogen bond with the NH group. It can then be argued that the two TMS groups of compound **4** and/or solvent effects force the predominance of a much different conformer to that of compound **3** in the solid state, where the 6-OH becomes more accessible. Table 1 contains the dihedral angles, measured from the structure of Figure 3,

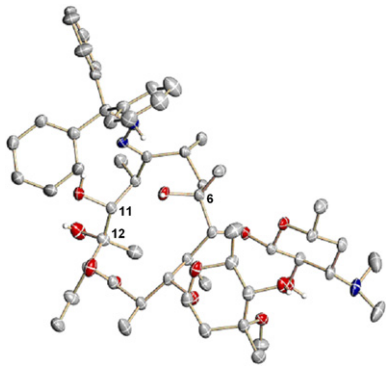

Fig. 3. X-ray structure of compound **3**.

Table 1
Dihedral angles between the indicated proton pairs obtained from the X-ray structure of compound **3** (Fig. 3) and calculated from the ^3J coupling constants (Hz) measured in compound **4** dissolved in DMSO-d_6

H(x),H(y)	Angle (X-ray)	$^3J_{calc}$	$^3J_{obs}$ DMSO-d_6	Calc. angle
2,3	177	9.9	**7.2**	**140**
3,4	−64	1.3	1.3	−64
4,5	126	5.0	**6.8**	**137**
7a,8	−82	1.1	**4.1**	**−55**
7b,8	162	11.2	**9.3**	**150**
10,11	72	0.9	0.9	72
13,14a	63	1.9	2.4	55
13,14b	180	11.5	11.1	187

that the indicated protons of the macrolide ring sustain. These angles are compared to the calculated ones (Janocchio program[11] with built-in Altona's equation) from the first-order interproton coupling constants of compound **4** in DMSO-d_6. The table indicates (numbers in bold) that in fact some dihedral angles have slightly changed from the solid state to solution in DMSO-d_6. However, molecular mechanics calculation (MM+, HYPERCHEM program) of compound **4** (restricting the angles calculated from the observed ^3J values in DMSO-d_6 and performing a conformational search around the four dihedral angles linking the two pyrane rings to the macrolide) led to a global most stable conformer of the 14-membered ring that is not very different, assuming some conformational libration, to that of the solid state structure of compound **3**, as it is shown in Figure 4. Therefore, ^{1}H NMR ^3J couplings are compatible with a structure of compound **4** in the polar solvent similar to that of compound **3** in the solid state (Fig. 3) where the 6-OH group appears to be quite hindered (see Fig. 5).

The single-point AM1 semiempirical HYPERCHEM calculation of compound **4** rendered a 3D mapped isosurface plot of total charge density that places 6-OH group within a non-polar narrow pocket. The hydroxyl groups at positions 11 and 12 are in turn reasonably exposed to the exterior. Therefore, the complete regioselectivity observed in the methylation of compound **4** should be attributed to solvation, in that strong association of 11- and 12-OH with the polar solvent presumably prevents them from being

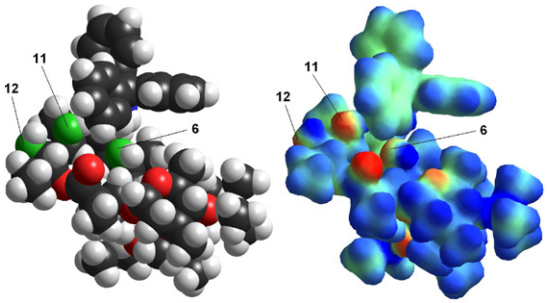

Fig. 5. CPK representation (left) and 3D mapped isosurface plot of total charge density (right) of compound **4**.

alkylated. Hydroxide ion and methyl iodide would have the right size to freely access the aforementioned pocket and thus react with 6-OH. Therefore, our results give, for the first time, strong experimental support to this hypothesis which was theoretically anticipated by other authors in 9-oxime derivatives but, unfortunately, considering the wrong stereochemistry at the C=N bond.[12]

Deprotection of 2′- and 4″-OH groups of **5** was fast and quantitative with formic acid in water–ethanol leading to 9-tritylhydrazone clarithromycin **6**.[13] We were also able to crystallize this compound whose X-ray structure is depicted in Figure 6. The use of sodium nitrite in slightly different conditions (water–acetonitrile instead of ethanol) led to the target clarithromycin **1** by the one-pot liberation of the 9-ketone and 2′- and 4″-OH groups in very good isolated yield. NMR and HPLC analysis of the crude and recrystalized clarithromycin **1** obtained by the method of Scheme 1 showed it to be free from polymethylated products which are common impurities in the reaction of other protected erythromycin derivatives. Moreover, trace quantities (ppb) of the strong UV-absorbing triphenylmethane (by-product of the last step) were easily detected by HPLC thus conferring a fingerprint to the described synthetic method in terms of the possible patent infringement.

Finally, compound **5** was further methylated at 12-OH with a stronger base (NaH; cf. Scheme 1) to give the dimethylated product **7**,[14] which was deprotected in identical conditions to those of **5** to render **8**.[15]

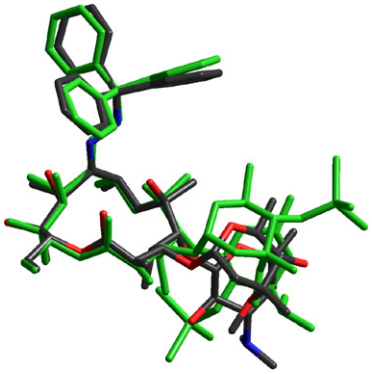

Fig. 4. Superimposed structures (hydrogen atoms have been omitted) of compounds **3** (from X-ray data) and **4** (green, from ^{1}H NMR and molecular mechanics calculation; see text).

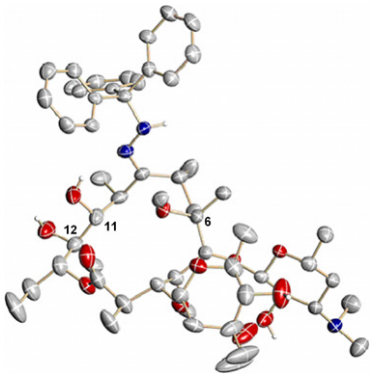

Fig. 6. X-ray structure of compound **6**.

In conclusion, the pursued objective of developing original methods for clarithromycin synthesis, allowing its high-scale production without infringing any of the existing patents, has been fully and successfully achieved for a second time.[8] To this effect, the novel erythromycin A 9-tritylhydrazone was prepared very easily in high yields from erythromycin A. Relatively non-stringent conditions were described to attain its regioselective methylation at 6-OH and a deprotection protocol was given to obtain clarithromycin in an excellent overall yield which has successfully been scaled up to multi-kilogram amounts. The deleterious methylation of hydroxyl groups at 11 and 12 positions, that occurred in other erythromycin A derivatives, was avoided by the bulky tritylhydrazone group, even with large excesses of KOH and MeI. Conformational evidence based on X-ray diffraction, ^{1}H NMR, and molecular mechanics calculations suggests an important role of solvation in the observed regioselectivity. Yet, by changing the base to NaH, the 6,12-O-dimethylated product was easily produced for the first time, thus leading to the completion of the necessary standards for assessing the quality of clarithromycin samples by HPLC methods or other techniques.[16]

References and notes

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5. Compound **3**: Mp 138–141 °C; $[\alpha]_D^{25}$ −53.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.20 (br s, 2H, NH_2), 5.07 (dd, 1H, $J = 2.3$, 10.9, C(13)*H*), 4.91 (d, 1H, $J = 4.7$, C(1″)*H*), 4.43 (d, 1H, $J = 7.2$, C(1′)*H*), 3.98–4.05 (m, 2H, C(3)*H*, C(5″)*H*), 3.46–3.59 (m, 3H, C(5)*H*, C(11)*H*, C(5′)*H*), 3.30 (s, 1H, C(8″)OCH_3), 3.16–3.27 (m, 2H, C(8)*H*, C(2′)*H*), 3.01 (t, 1H, $J = 8.9$, C(4″)*H*), 2.86 (br s, 1H, O*H*), 2.83 (q, 1H, $J = 7.3$, C(2)*H*), 2.64 (q, 1H, $J = 7.1$, C(10)*H*), 2.45 (ddd, 1H, $J = 3.9$, 10.6, 12.2, C(3′)*H*), 2.36 (d, 1H, $J = 15.0$, C(2″)H_b), 2.28 (s, 6H, N(CH_3)$_2$), 2.20 (d, 1H, $J = 12.9$, O*H*), 1.98 (ddd, 1H, $J = 1.8$, 2.6, 7.8, C(4)*H*), 1.91 (ddq, 1H, $J = 2.2$, 7.4, 15.2, C(14)H_b), 1.63–1.72 (m, 2H, C(7)H_a, C(4′)H_b), 1.57 (dd, 1H, $J = 5.0$, 15.1, C(2″)H_a), 1.51 (m, 1H, C(14)H_a), 1.44 (s, 3H, C(6)H_3), 1.28 (d, 3H, $J = 6.1$, C(5″)H_3), 1.24 (m, 1H, C(4′)H_a), 1.23 (s, 3H, C(3″)H_3), 1.22 (d, 3H, $J = 6.1$, C(5′)H_3), 1.18 (d, 3H, $J = 7.3$, C(2)H_3), 1.13 (d, 3H, $J = 6.2$, C(4)H_3), 1.12 (s, 3H, C(12)H_3), 1.11 (d, 3H, $J = 7.1$, C(10)H_3), 1.06 (d, 3H, $J = 7.1$, C(8)H_3), 0.83 (t, 3H, $J = 7.7$ Hz, C(14)H_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.5, 168.0, 103.1, 96.6, 83.8, 79.8, 77.8, 77.1, 75.0, 74.1, 72.6, 71.5, 70.8, 68.9, 65.7, 65.4, 49.4, 45.0, 40.3, 39.9, 38.4, 35.0, 33.0, 28.6, 26.8, 26.1, 21.4, 21.3, 21.1, 18.9, 18.5, 16.1, 15.9, 13.9, 10.7, 9.4.
6. Compound **4**: Mp 118–120 °C; $[\alpha]_D^{25}$ −47.7 (*c* 0.012, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.19–7.31 (m, 15H, *H*-arom), 6.73 (br s, 1H, N*H*), 5.04 (d, 1H, $J = 4.9$, C(1″)*H*), 4.90 (dd, 1H, $J = 2.5$, 10.8, C(13)*H*), 4.50 (br s, 1H, C(3)*H*), 4.36 (d, 1H, $J = 7.2$, C(1′)*H*), 4.20 (dq, 1H, $J = 2.8$, 6.3, C(5″)*H*), 3.91 (s, 2H, 2 × O*H*), 3.58 (m, 2H, C(8)*H*, C(5′)*H*), 3.50 (d, 1H, $J = 9.2$, C(5)*H*), 3.29 (s, 3H, C(3″)OCH_3), 3.22 (dd, 1H, $J = 7.1$, 9.8, C(2′)*H*), 3.11, (s, 1H, C(11)*H*), 3.07 (br s, 1H, O*H*), 3.05 (d, 1H, $J = 9.0$, C(4″)*H*), 2.60 (m, 2H, C(2)*H*, C(10)*H*), 2.59 (ddd, 1H, $J = 2.1$, 4.3, 9.8, C(3′)*H*), 2.46 (d, 1H, $J = 15.2$, C(2″)H_b), 2.30 (s, 6H, N(CH_3)$_2$), 1.88 (m, 2H, C(4)*H*, C(14)H_b), 1.68 (m, 2H, C(7)H_b, C(4′)H_b), 1.53 (dd, 1H, $J = 5.1$, 15.3, C(4″)H_b), 1.41 (s, 4H, C(7)H_a, C(6)CH_3), 1.37 (m, 1H, C(14)H_a), 1.20 (d, 3H, $J = 7.8$ Hz, C(2)CH_3), 1.16 (d, 4H, $J = 6.3$, C(5′)H_3, C(4′)H_a), 1.14 (s, 3H, C(3″)CH_3), 1.10 (s, 3H, C(12)CH_3), 1.08 (d, 6H, $J = 6.3$, C(4)CH_3), 1.07 (d, 6H, $J = 6.3$, C(8)CH_3), 0.95 (d, 3H, $J = 6.8$, C(10)CH_3), 0.84 (t, 3H, $J = 7.8$, C(14)CH_3), 0.78 (d, 3H, $J = 6.3$, C(5″)CH_3), 0.16 (s, 9H, Si(CH_3)$_3$), 0.14 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.1 165.1, 146.5, 129.1, 128.4, 127.7, 127.6, 103.2, 97.8, 81.9, 80.5, 79.4, 77.9, 75.6, 74.0, 73.3, 72.9, 71.8, 68.4, 65.3, 65.1, 49.7, 43.4, 40.9, 38.7, 35.7, 33.4, 30.3, 27.6, 27.4, 22.0, 21.3, 21.2, 18.3, 16.4, 15.0, 13.4, 10.9, 10.1.
7. Compound **5**: Mp 84–86 °C; $[\alpha]_D^{25}$ −46.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.22–7.38 (m, 15H, *H*-arom), 5.61 (s, 1H, N*H*), 5.15 (dd, 1H, $J = 2.5$, 11.4, C(13)*H*), 4.99 (d, 1H, $J = 5.4$, C(1″)*H*), 4.67 (s, 1H, O*H*), 4.51 (d, 1H, $J = 7.0$, C(1′)*H*), 4.29 (dq, 1H, $J = 6.4$, 9.2, C(5″)*H*), 3.83 (dd, 1H, $J = 1.3$, 9.7, C(3)*H*), 3.80 (d, 1H, $J = 6.8$, C(5)*H*), 3.73 (ddq, 1H, $J = 2.0$, 6.0, 11.1, C(5′)*H*), 3.59–3.66 (m, 2H, C(11)*H*, O*H*), 3.36 (s, 3H, C(3″)OCH_3), 3.30 (s, 3H, C(6)OCH_3), 3.25 (s, 1H, O*H*), 3.21 (d, 1H, $J = 9.2$, C(4″)*H*), 3.13–3.19 (m, 2H, C(8)*H*, C(2′)*H*), 2.94 (m, 1H, C(2)*H*), 2.56 (ddd, 1H, $J = 2.2$, 9.7, C(3′)*H*), 2.37–2.50 (m, 2H, C(10)*H*, C(2″)H_a), 2.26 (s, 6H, N(CH_3)$_2$), 1.93 (m, 2H, C(4)*H*, C(14)H_a), 1.63–1.73 (m, 2H, C(7)H_a, C(4′)H_a), 1.53–1.61 (m, 2H, C(7)H_b, C(2″)H_b), 1.50 (s, 3H, C(6)CH_3), 1.45 (m, 1H, C(14)H_b), 1.28 (d, 3H, $J = 6.3$, C(5″)CH_3), 1.26 (d, 3H, $J = 6.9$, C(2)CH_3), 1.22 (d, 3H, $J = 6.0$, C(5′)CH_3), 1.21 (s, 3H, C(3″)CH_3), 1.18 (m, 1H, C(4′)H_b), 1.13 (s, 3H, C(12)CH_3), 1.11 (d, 3H, $J = 6.8$, C(4)CH_3), 0.87 (t, 3H, $J = 6.9$, C(14)CH_3), 0.82 (d, 3H, $J = 6.9$, C(8)CH_3), 0.67 (d, 3H, $J = 6.9$, C(10)H_3), 0.19 (s, 9H, Si(CH_3)$_3$), 0.12 (s, 9H, Si(CH_3)$_3$).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.4, 165.0, 145.9, 143.9, 128.7, 128.6, 128.3, 128.9, 127.8, 127.7, 126.8, 126.4, 102.3, 96.2, 87.0, 80.7, 79.1, 79.09, 78.2, 76.8, 73.9, 73.3, 73.1, 72.9, 67.0, 65.3, 65.1, 52.0, 51.7, 49.6, 46.1, 45.2, 41.0, 38.8, 37.8, 35.8, 32.8, 29.4, 26.5, 22.2, 22.0, 21.1, 20.7, 19.5, 19.1, 16.3, 16.1, 14.5, 10.4, 10.0, 1.0, 0.9.
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13. Compound **6**: Mp 238–240 °C; $[\alpha]_D^{25}$ −50.4 (*c* 0.098, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.17–7.41 (m, 15H, *H*-arom), 5.56 (s, 1H, N*H*), 5.12 (dd, 1H, $J = 2.3$, 11.2, C(13)*H*), 4.97 (d, 1H, $J = 4.4$, C(1″)*H*), 4.66 (s, 1H, O*H*), 4.50 (d, 1H, $J = 7.2$, C(1′)*H*), 4.04 (dq, 1H, $J = 6.2$, 8.9, C(5″)*H*), 3.80 (d, 1H, $J = 6.5$, C(5)*H*), 3.74 (dd 1H, $J = 1.6$, 10.0, C(3)*H*), 3.57 (d, 1H, $J = 1.3$, C(11)*H*), 3.53 (m, 1H, C(5′)*H*), 3.33 (s, 3H, C(3″)OCH_3), 3.27 (s, 3H, C(6)OCH_3), 3.16–3.24 (m, 2H, C(2′)*H*, O*H*), 3.11 (m, 1H, C(8)*H*), 3.01 (m, 1H, C(4″)*H*), 2.95 (dq, 1H, $J = 1.9$, 7.9, C(2)*H*), 2.44 (m, 1H, C(10)*H*), 2.42 (d, 1H, $J = 14.8$, C(2″)H_b), 2.29 (s, 6H, N(CH_3)$_2$), 2.21 (br s, 1H, O*H*), 1.98 (q, 1H, $J = 7.2$, C(4)*H*), 1.85 (m, 1H, C(14)CH_b), 1.68 (m, 1H, C(7)H_b), 1.61 (dd, 1H, $J = 4.7$, 14.5, C(4′)H_a), 1.52 (d, 1H, $J = 13.6$, C(7)H_a), 1.47 (s, 3H, C(6)CH_3), 1.43 (m, 1H, C(14)H_a), 1.32 (d, 3H, $J = 6.3$, C(5″)CH_3), 1.26 (s, 3H, C(3″)CH_3), 1.19–1.25 (m, 7H, C(2)CH_3, C(4′)H_a, C(5′)CH_3), 1.04 (s, 3H, C(12)CH_3), 0.82 (t, 3H, $J = 7.6$, C(14)CH_3), 0.77 (d, 3H, $J = 7.6$, C(8)CH_3), 0.62 (d, 3H, $J = 7.6$, C(10)CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.0, 164.9, 145.9, 128.9, 128.0, 127.9, 127.8, 126.4, 102.4, 96.2, 79.6, 78.8, 78.7, 77.9, 76.9, 73.9, 72.9, 72.7, 71.1, 70.8, 67.9, 65.8, 65.5, 51.9, 49.4, 45.0, 40.3, 38.3, 37.5, 35.0, 32.8, 26.6, 25.6, 21.6, 21.5, 21.1, 20.5, 19.2, 18.7, 16.2, 16.1, 14.5, 10.4, 9.3.
14. Compound **7**: Mp 80–82 °C; $[\alpha]_D^{25}$ −36.8 (*c* 0.102, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.16–7.53 (m, 15H, *H*-arom), 5.63 (dd,

1H, $J = 1.9$, 11.7, C(13)H), 5.59 (s, 1H, NH), 4.98 (d, 1H, $J = 5.0$, C(1″)H), 4.49 (d, 1H, $J = 6.6$, C(1′)H), 4.29 (dq, 1H, $J = 6.3$, 9.2, C(5″)H), 3.91 (s, 1H, OH), 3.77–3.85 (m, 2H, C(3)H, C(5)H), 3.72 (m, 1H, C(5′)H), 3.36 (s, 3H, C(3″)OCH_3), 3.34 (s, 3H, C(12)OCH_3), 3.25 (s, 3H, C(6)OCH_3), 3.13–3.24 (m, 4H, C(8)H, C(11)H, C(2′)H, C(4″)H), 2.95 (m, 1H, C(2)H), 2.50–2.61 (m, 2H, C(10)H, C(3′)H), 2.36–2.47 (m, 1H, C(2″)CH_a), 2.26 (s, 6H, N(CH_3)$_2$), 1.95 (m, 1H, C(4)H), 1.80 (m, 1H, C(14)CH_a), 1.61–1.74 (m, 2H, C(7)H_b, C(4′)H_b), 1.52–1.60 (m, 3H, C(7)H_a, C(14)H_b, C(2″)H_b), 1.49 (s, 3H, C(6)CH_3), 1.28 (d, 3H, $J = 6.0$, C(5″)CH_3), 1.26 (d, 3H, $J = 7.2$, C(2)CH_3), 1.24 (m, 1H, C(4′)H_b), 1.22 (d, 3H, $J = 6.0$, C(5′)CH_3), 1.21 (s, 3H, C(3″)CH_3), 1.12 (d, 3H, $J = 7.2$, C(4)CH_3), 1.11 (s, 3H, C(12)CH_3), 0.91 (t, 3H, $J = 7.2$, C(14)CH_3), 0.84 (d, 3H, $J = 7.2$, C(8)CH_3), 0.71 (d, 3H, $J = 7.0$, C(10)CH_3), 0.20 (s, 9H, Si(CH_3)$_3$), 0.12 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 174.6, 164.5, 147.0, 146.1, 128.9, 128.7, 128.3, 127.7, 127.5, 127.4, 126.9, 126.8, 126.2, 102.3, 96.4, 80.7, 80.7, 79.2, 79.0, 78.4, 75.5, 73.4, 73.1, 72.9, 72.8, 67.1, 65.2, 52.7, 51.7, 49.6, 45.0, 40.9, 38.7, 37.9, 35.9, 31.4, 29.6, 29.5, 26.4, 22.2, 22.0, 21.5, 20.6, 19.5, 19.2, 16.2, 15.5, 13.8, 10.4, 10.1, 1.0, 0.8.

15. Compound **8**: Mp 112–115 °C; $[\alpha]_D^{25}$ −95.49 (c 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.52 (dd, 1H, J= 1.6, 11.0, C(13)H), 4.90 (d, 1H, $J = 5.1$, C(1″)H), 4.40 (d, 1H, $J = 7.2$, C(1′)H), 3.98 (dq, 1H, $J = 6.1$, 9.3, C(5″)H), 3.76 (dd, 1H, $J = 1.3$, 3.4, C(3)H), 3.73 (dd, 1H, $J = 0.9$, 9.6, C(11)H), 3.64 (d, 1H, $J = 7.5$, C(5)H), 3.46 (m, 1H, C(5′)H), 3.43 (s, 3H, C(12)OCH_3), 3.35 (d, $J = 3.5$, OH), 3.30 (s, 3H, C(3″)OCH_3), 3.16 (dd, 1H, $J = 3.0$, 7.3, C(2′)H), 3.08 (m, 1H, C(10)H), 3.06 (s, 4H, C(6)OCH_3), 2.96–3.03 (m, 2H, C(4″)H, OH), 2.89 (dq, 1H, $J = 2.4$, 7.3, C(2)H), 2.60–2.70 (m, 1H, C(8)H), 2.37–2.44 (m, 1H, C(3′)H), 2.34 (d, 1H, $J = 15.7$, C(2″)H_a), 2.27 (s, 6H, N(CH_3)$_2$), 2.20 (br s, 1H, OH), 1.83–1.92 (m, 1H, C(4)H), 1.69–1.80 (m, 2H, C(7)H_a, C(14)H_a), 1.60–1.69 (m, 2H, C(7)H_b, C(4′)H_a), 1.48–1.60 (m, 2H, C(14)H_b, C(2″)H_b), 1.39 (s, 3H, C(6)CH_3), 1.28 (d, 3H, $J = 6.2$, C(5″)CH_3), 1.21–1.25 (s, 4H, C(12)CH_3, C(4′)H_b), 1.20 (d, 3H, $J = 6.3$, C(10)CH_3), 1.18 (d, 3H, $J = 6.7$, C(5′)CH_3), 1.18 (d, 3H, $J = 6.6$, C(2)CH_3), 1.11 (d, 3H, $J = 7.0$, C(8)CH_3), 1.07 (d, 3H, $J = 8.3$, C(4)CH_3), (s, 3H, C(12)CH_3), 0.88 (t, 3H, $J = 7.3$, C(14)CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 218.7, 175.7, 102.7, 96.3, 81.0, 79.3, 78.8, 78.6, 77.9, 74.9, 72.7, 71.4, 70.9, 68.1, 65.7, 65.3, 53.2, 50.9, 49.4, 45.1, 43.7, 40.9, 39.8, 39.0, 38.9, 34.9, 29.8, 21.4, 21.3, 21.2, 20.0, 18.7, 18.4, 17.1, 15.9, 11.2, 10.5, 9.2.

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