An Efficient and Straightforward Method to New Organic Compounds: Homodrimane Sesquiterpenoids with Diazine Units

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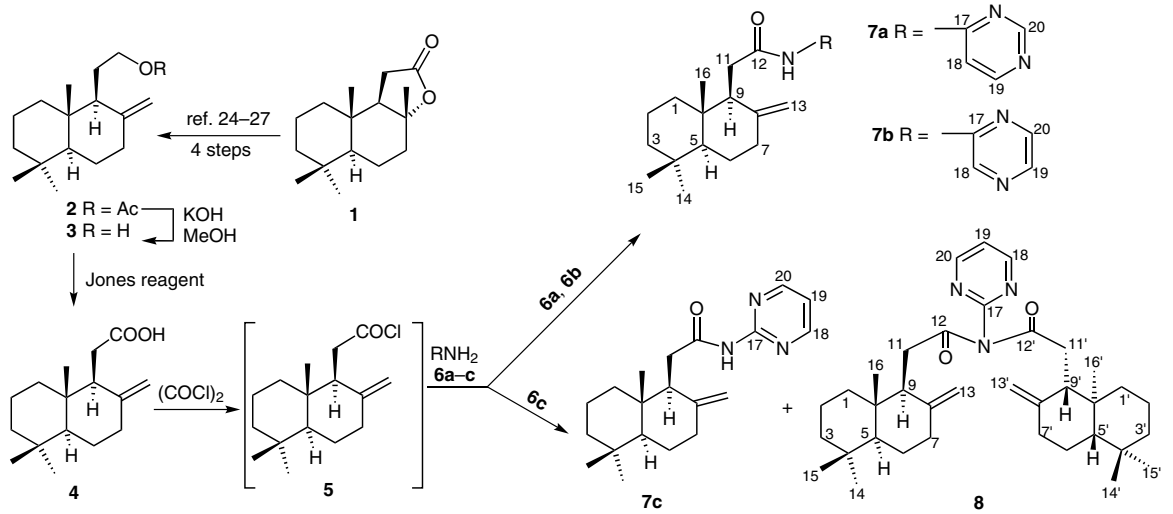
Abstract: A comprehensive study of the synthesis and structure of new homodrimane sesquiterpenoids with diazine skeleton is presented. This is the first synthesis of homodrimane sesquiterpenoids with diazine skeleton. In the same time, an efficient way for the one-pot bisacylation of 2-aminopyrimidine is reported. The structure of the bisacylamide was proven unambiguously, including the single-crystal X-ray structure determination. A reliable explication and feasible reaction mechanisms for the obtained compounds are presented.

Key words: homodrimane, sesquiterpenoids, diazine, one-pot bisacylation, bisacylamide

Sesquiterpenoids, especially those with a drimane skeleton, are natural or synthetic compounds with a wide application in medicine, pharmaceutics, cosmetics, and agriculture.[1–3] A special attention was paid to natural and synthetic drimane products with biological activity, particularly those with anticancer, antimicrobial, antifungal, etc. activities[1,2,4–7] On the other hand, fused and nonfused diazines have proved to be invaluable materials for medicine, pharmaceutics, optoelectronics, and agriculture.[8–10] These compounds exhibit a large variety of biological activities, such as antimicrobial, antifungal, antituberculosis, antiviral, anti-HIV, anticancer, etc.[10–17] N-Acylation of amino diazines has attracted special attention of scientists engaged in organic synthesis because of the pharmacological importance of the products.[18,19] To the best of our knowledge there is only one example for the bisacylation of amino diazines (2-aminopyrimidine) described in the literature.[20]

In continuation of our work in the field of drimane sesquiterpenoids[21–23] and azaheterocycles[10,11,13,14,16] with potential practical applications, we report herein our preliminary results on the synthesis of new homodrimane sesquiterpenoids with diazine skeleton.

As a starting material for the synthesis of our compounds was used bicyclohomofarnezenic acid (**4**) (obtained from commercially available sclareolide (**1**) in six steps with an overall yield 60%,[24–27] Scheme 1). Two strategies were then adopted in order to synthesize the bicyclohomofarnezenic acid amides **7a–c**. Using method I[29] the bicyclohomofarnezenic acid chloride (**5**, generated in situ from acid **4**) was treated with the corresponding amines **6a–c**



Scheme 1 Reaction pathway for preparation of homodrimane sesquiterpenoids with diazine skeleton – method I

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(4-aminopyrimidine, aminopyrazine, and 2-aminopyrimidine), leading to the desired products (Scheme 1).

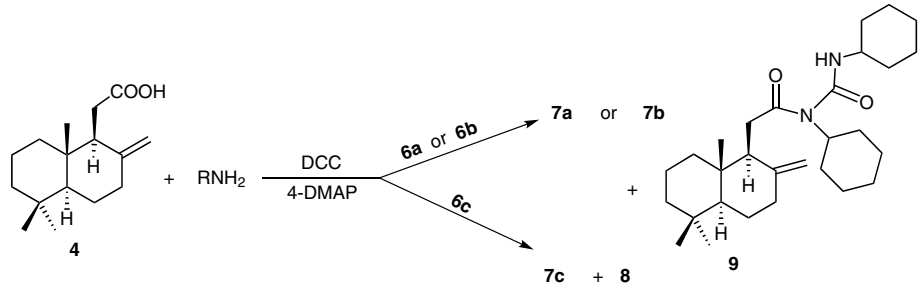
In the case of 4-aminopyrimidine (**6a**) and aminopyrazine (**6b**), only the monoacyl amide **7a** and **7b** were obtained. However, on the interaction of the acid chloride **5** and 2-aminopyrimidine (**6c**) besides the monoacyl amide **7c** the bisacylamide **8** was formed as a principal product.

In order to ascertain if the bisacylation reaction of 2-aminopyrimidine could take place under any conditions, and also with the purpose of the increasing of reaction yields, we performed the acylation using another synthetic route (method II, Scheme 2).[30]

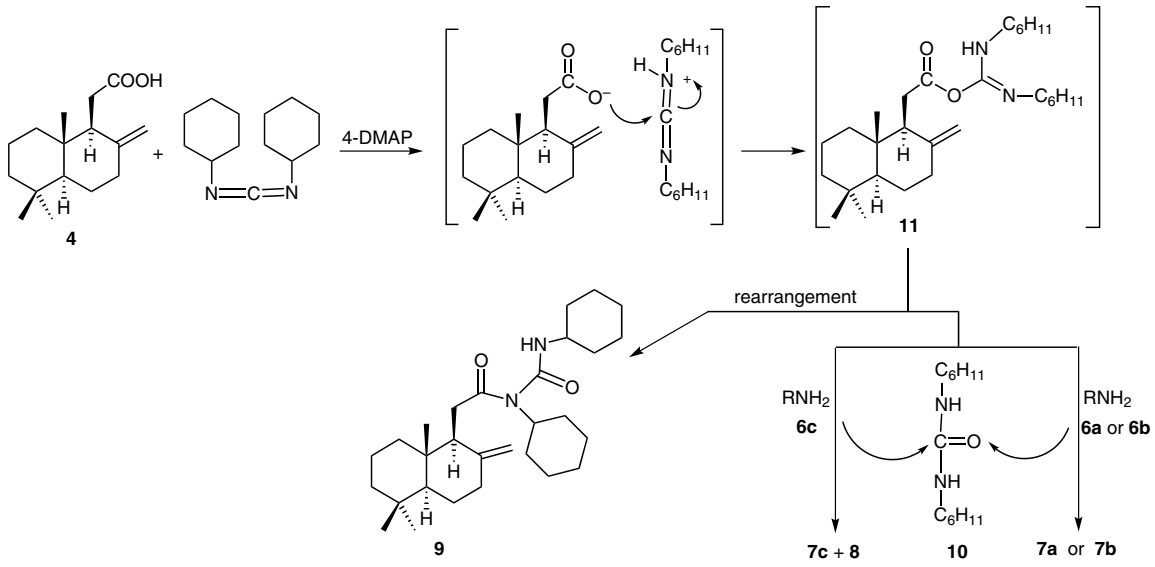
In this method the acid **4** was treated directly with the corresponding amines **6a**–**c** in the presence of dicyclocarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). In this synthetic pathway, besides the desired amides **7a**–**c**[31] and **8**,[28,32] another new compound, *N*-Δ^{8,13}-bicyclohomofarnezenoyl-*N*,*N*′-dicyclohexylurea (**9**), was prepared. Moreover, the formation of the byproduct, *N*,*N*′-dicyclohexylurea **10**,[33] makes the situation even more difficult. The formation of compounds **9** and **10** could be explained through the following reaction mechanism: after the initial protonation of one nitrogen from DCC, a nucleophilic attack of the carboxyl ion generated the intermediate **11**. The substituted urea **9** was then generated as a result of a rearrangement process of this compound, while *N*,*N*′-dicyclohexylurea **10** was produced as a byproduct on the interaction of the intermediate **11** with amines **6a**–**c** (Scheme 3).

The summary of the product yields, resulting from the two methods of acylation, is given in Table 1.

It is to be pointed out that the bisacylation process took place only in the case of 2-aminopyrimidine. No doubt that this is a question of the placement of the amino group between the two nitrogen atoms (which have an electron-



Scheme 2 Reaction pathway for preparation of homodrimane sesquiterpenoids with diazine skeleton – method II



Scheme 3 Proposed reaction mechanism for the synthesis of homodrimane sesquiterpenoids with diazine skeleton through method II

Table 1 Yields and Products Obtained in the Acylation Reactions of Amines **6a**–**c**

Method	Compound and yield		
I	**7a** 60%	**7b** 15%	**7c** 16% + **8** 54%
II	**7a** 53% + **9** 20%	**7b** 52% + **9** 17%	**7c** 22% + **8** 33% + **9** 22%

withdrawing effect) of the pyrimidine ring, which activates the amino group. As a result, this amino group could be bisacylated.

The structures of all new compounds were proved unambiguously by elemental and spectral analysis [IR, ^{1}H NMR, ^{13}C NMR, two-dimensional experiments 2D-COSY, 2D-HETCOR (HMQC), long-range 2D-HETCOR (HMBC)], and finally, in the case of the bisacylamide **8**, also through single-crystal X-ray structure determination (Figure 1).

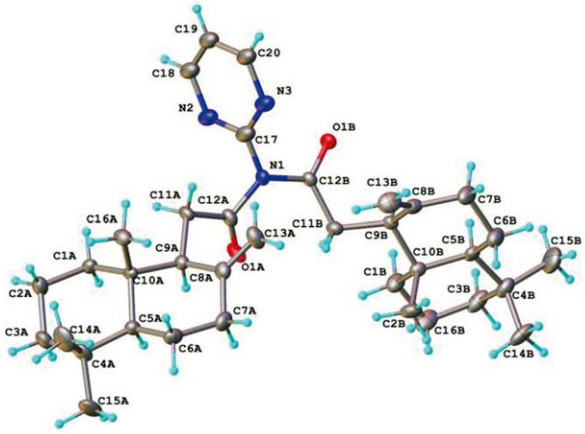


Figure 1 ORTEP representation at 40% probability for compound **8** including atom-numbering scheme

In conclusion, we report herein an efficient and straightforward route for the synthesis of new homodrimane sesquiterpenoids with diazine skeleton. Two acylation procedures were used for the synthesis of our derivatives: acylation with acyl chlorides and acylation with organic acids. The acylation of aminodiazine with acyl chlorides proved to be more efficient. The structure of compounds was proven unambiguously by elemental and spectral analysis, in the case of bisacylamide **8** also through single-crystal X-ray structure determination. A reliable explication and feasible reaction mechanism for the obtained compounds is presented. On our knowledge, this is the first example of a homodrimane sesquiterpenoid with diazine skeleton and also the first example of an efficient way for the one-pot bisacylation of aminodiazine.

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References and Notes

(1) Zhan, Z. J.; Ying, Y. M.; Ma, L. F.; Shan, W. G. *Nat. Prod. Rep.* **2011**, *28*, 594.
(2) Jansen, B. J. M.; de Groot, A. *Nat. Prod. Rep.* **2004**, *21*, 449.
(3) Choudhary, M. I.; Musharraf, S. G.; Sami, A.; Atta-ur-Rahman *Helv. Chim. Acta* **2004**, *87*, 2685.
(4) Allouche, N.; Apel, C.; Martin, M. T.; Dumontet, V.; Guéritte, F.; Litaudon, M. *Phytochemistry* **2009**, *70*, 546.
(5) Zhou, H.; Zhu, T.; Cai, S.; Gu, Q.; Li, D. *Chem. Pharm. Bull.* **2011**, *59*, 762.
(6) Ying, B. P.; Peiser, G. D.; Ji, Y.-Y.; Mathias, K. M.; Karasina, F.; Hwang, Y. S. *J. Agric. Food Chem.* **1995**, *43*, 826.
(7) Nelson, Z.; Georges, L.; Guy, S. *Pest Manage Sci.* **2010**, *66*, 1324.
(8) Achelle, S.; Plé, N. *Curr. Org. Synth.* **2012**, *9*, 163.
(9) Achelle, S.; Barsella, A.; Baudequin, C.; Bertrand, C.; Françoise, R. G. *J. Org. Chem.* **2012**, *77*, 4087.
(10) Mangalagiu, I. I. *Curr. Org. Chem.* **2011**, *15*, 730.
(11) Zbancioc, A. M.; Zbancioc, G.; Tanase, C.; Miron, A.; Ursu, C.; Mangalagiu, I. I. *Lett. Drug Des. Discovery* **2010**, *7*, 644.
(12) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140.
(13) Butnariu, R.; Mangalagiu, I. I. *Bioorg. Med. Chem.* **2009**, *17*, 2823.
(14) Balan, A. M.; Florea, O.; Moldoveanu, C.; Zbancioc, G.; Iurea, D.; Mangalagiu, I. I. *Eur. J. Med. Chem.* **2009**, 2275.
(15) Yves, L. J. *Bioorg. Med. Chem.* **2007**, *15*, 2479.
(16) Moldoveanu, C.; Mangalagiu, I. I. *Helv. Chim. Acta* **2005**, *88*, 2747.
(17) De Clercq, E. *J. Med. Chem.* **2005**, *48*, 1297.
(18) Culf, A. S.; Melanson, J. A.; Ouellette, R. J.; Briand, G. G. *Tetrahedron Lett.* **2012**, *53*, 3301.
(19) Katritzky, A. R.; Suzuki, K.; Singh, S. K. *ARKIVOC* **2004**, *(i)*, 12.
(20) Morizzo, E.; Capelli, F.; Lenzi, O.; Catarzi, D.; Varano, F.; Filacchioni, G.; Vincenzi, F.; Varani, K.; Andrea Borea, P.; Colotta, V.; Moro, S. *J. Med. Chem.* **2007**, *50*, 6596.
(21) Kuchkova, K. I.; Arîcu, A. N.; Barba, A. N.; Vlad, P. F.; Lipkovskii, J.; Simonov, Yu. S.; Kravtov, V. K. *Chem. Nat. Comp.* **2011**, *47*, 223.
(22) Kuchkova, K. I.; Aricu, A. N.; Vlad, P. F.; Deleanu, C.; Nicolescu, A. *Chem. Nat. Comp.* **2010**, *46*, 539.
(23) Kuchkova, K. I.; Aricu, A. N.; Vlad, P. F. *Chem. Nat. Comp.* **2009**, *45*, 367.
(24) Martres, P.; Perfetiti, P.; Zahra, J.-P.; Waegell, B.; Giraudi, E.; Petrzilka, M. *Tetrahedron Lett.* **1993**, *34*, 629.
(25) Vlad, P. F.; Dragalina, G. A.; Coltsa, M. N. *Russ. J. Gen. Chem.* **1977**, *47*, 943.
(26) Vlad, P. F.; Ungur, N. D.; Aricu, A. N.; Andreeva, I. Y. *Russ. Chem. Bull.* **1997**, *46*, 800.
(27) Martres, P.; Perfetiti, P.; Zahra, J.-P.; Waegell, B. *Tetrahedron Lett.* **1993**, *34*, 3127.
(28) The crystal structure for compound **8** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 893824. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or email: deposit@ccdc.cam.ac.uk].
(29) **Typical Procedure for the Synthesis of Bicyclohomofarnezenic Acid Derivatives with Diazine Skeleton – Method I**
To a solution of the acid **4** (200 mg, 0.80 mmol) in anhydrous benzene (4 mL) a solution of $(COCl)_2$ (0.8 mL, 1.16 g, 9.17 mmol) in anhydrous benzene (2 mL) was added. Then the reaction mixture was stirred at r.t. for 1 h and then refluxed (1 h). Benzene and excess $(COCl)_2$ were evaporated under reduced pressure. To the residue CH_2Cl_2 (8 mL) and aminodiazine **6a–c** (1.26 mmol) were added, and the resulting mixture was heated (40 °C) under stirring for an appropriate period of time [2 h for 4-aminopyrimidine (**6a**), 5 h for aminopyrazine (**6b**), 15 h for 2-aminopyrimidine (**6c**)]. A precipitate was filtered off, washed with CH_2Cl_2, and the filtrate was concentrated to dryness. The residue was dissolved in $CHCl_3$ (3 mL) and was purified by flash

chromatography on silica ($CHCl_3$). The following supplementary operations and remarks were to be pointed out in the case of reaction products derived from amine **6c**: elution with $CHCl_3$ afforded gradually the bisacylamide **8**, the monoacyl amide **7c**, and a two-component mixture. This mixture was subject to a second flash over silica (PE–Et_2O, 8:2) when monoacyl amide **7c** and some unreacted acid **4** were separated.

(30) **Typical Procedure for the Synthesis of Bicyclohomofarnezenic Acid Derivatives with Diazine Skeleton – Method II**

A solution of DCC (215 mg, 1.04 mmol), DMAP (100 mg, 0.82 mmol), aminodiazine **6a–c** (0.84 mmol), and the acid **4** (100 mg, 0.40 mmol) in CH_2Cl_2 (4 mL) was stirred at r.t. for an appropriate period of time [10 h for 4-aminopyrimidine (**6a**), 28 h for aminopyrazine (**6b**), 5 h for 2-aminopyrimidine (**6c**)]. A precipitate was filtered off, washed with CH_2Cl_2, and the filtrate was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (5 mL) and was purified by flash chromatography on silica ($CHCl_3$). The following supplementary operations and remarks were to be pointed out in the case of reaction products derived from amine **6c**: elution with $CHCl_3$ gave a mixture of the bisacylamide **8** and the urea **9**. For the separation of these compounds, the mixture was extracted first with PE. The undissolved precipitate was filtered off and washed thoroughly with PE when the bisacylamide **8** was obtained. The filtrate solution was evaporated to dryness and the residue crystallized from MeCN giving urea **9**. The remaining silica from the first flash chromatography was washed with $CHCl_3$ affording a mixture of the monoacyl amide **7c** and dicyclohexylurea **10**. This mixture was extracted with Et_2O. The undissolved precipitate of dicyclohexylurea **10** was filtered off, and the ether filtrate was concentrated to dryness. The obtained residue was crystallized from MeCN to give the monoacyl amide **7c**.

(31) **$\Delta^{8,13}$-Bicyclohomofarnezenic Acid Amide (7c)**

White crystals; mp 149–150 °C. $[\alpha]_D^{26}$ –14.8 (*c* 0.6, $CHCl_3$). IR: 3262, 3189, 3111 (NH amide), 3078, 892 (semicyclic methylene), 1725 (C=O, amide), 1649, 1574, 1435, 1155 (pyrimidine cycle) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.60 (2 H, d, *J* = 8.0 Hz, H-18, H-20), 8.51 (1 H, br s, NH), 6.99 (1 H, t, *J* = 4.9 Hz, H-19), 4.79 (1 H, s, Ha-13), 4.54 (1 H, s, Hb-13), 2.95 (1 H, dd, *J* = 16.6, 10.1 Hz, Ha-11), 2.79 (1 H, dd, *J* = 16.6, 3.7 Hz, Hb-11), 2.56 (1 H, dd, *J* = 10.1, 3.7 Hz, H-9), 2.41 (1 H, ddd, *J* = 13.0, 4.0, 2.4 Hz, Ha-7), 2.15 (1 H, td, *J* = 13.0, 4.0 Hz, Hb-7), 1.26 (1 H, dd, *J* = 12.6, 2.1 Hz, H-5), 1.80–1.10 (8 H, m), 0.90 (3 H, s, H-14), 0.83 (3 H, s, H-15), 0.76 (3 H, s, H-16). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.64 (s, C-12), 158.32 (d, C-20), 158.32 (d, C-18), 157.70 (s, C-17), 149.27 (s, C-8), 116.14 (d, C-19), 106.51 (t, C-13), 55.21 (d, C-5), 52.27 (d, C-9), 42.12 (t, C-3), 39.24 (s, C-10), 39.09 (t, C-1), 37.67 (t, C-7), 33.57 (q, C-14), 33.56 (t, C-11), 33.53 (s, C-4), 24.13 (t, C-6), 21.77 (q, C-15), 19.35 (t, C-2), 14.75 (q, C-16).

(32) **2-Bis-$\Delta^{8,13}$-bicyclohomofarnezenoylaminopyrimidine (8)**

White crystals; mp 205–206 °C. $[\alpha]_D^{26}$ 27.78 (*c* 0.33, $CHCl_3$). IR: 3088, 897 (semicyclic methylene), 1704 (C=O, amide), 1644, 1567, 1460, 1410, 1162 (pyrimidine cycle) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.87 (2 H, d, *J* = 4.9 Hz, H-18, H-20), 7.34 (1 H, t, *J* = 4.9 Hz, H-19), 4.80 (2 H, s, Ha-13, Ha-13′), 4.52 (2 H, s, Hb-13, Hb-13′), 2.72 (2 H, dd, *J* = 16.9, 2.6 Hz, Ha-11, Ha-11′), 2.56 (2 H, dd, 16.9, 10.2 Hz, Hb-11, Hb-11′), 2.49 (2 H, dd, *J* = 10.0, 2.0 Hz, H-9, H-9′), 2.39 (2 H, ddd, *J* = 13.0, 4.0, 2.3 Hz, Ha-7, Ha-7′), 2.10 (2 H, td, *J* = 13.0, 5.0, Hz, Hb-7, Hb-7′), 1.18 (2 H, dd, *J* = 12.5, 2.5 Hz, H-5, H-5′), 1.80–1.03 (16 H, m), 0.87 (6 H, s, H-14, H-14′), 0.79 (6 H, s, H-15, H-15′), 0.59 (6 H, s, H-16, H-16′). ^{13}C NMR (100 MHz,$CDCl_3$): δ = 175.22 (s, C-12), 159.95 (s, C-17), 159.34 (d, C-18), 159.34 (d, C-20), 148.92 (s, C-8), 120.20 (d, C-19), 106.41 (t, C-13), 55.12 (d, C-5), 51.90 (d, C-9), 42.05 (t, C-3), 39.03 (t, C-1), 38.90 (s, C-10), 37.54 (t, C-7), 34.38 (t, C-11), 33.56 (q, C-14), 33.49 (s, C-4), 23.97 (t, C-6), 21.73 (q, C-15), 19.25 (t, C-2), 14.63 (q, C-16).

(33) ***N*-$\Delta^{8,13}$-Bicyclohomofarnezenoyl-*N*,*N*′-Dicyclohexylurea (10)**

White crystals; mp 166–167 °C. $[\alpha]_D^{26}$ 11.9 (*c* 1.34, $CHCl_3$). IR: 3266 (NH amide), 3074, 879 (semicyclic methylene), 1698 (C=O amide), 1658 (C=O amide) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.47 (1 H, br s, NH), 4.75 (1 H, s, Ha-13), 4.43 (1 H, s, Hb-13), 4.02 (1 H, m, H-17), 3.72 (1 H, m, H-24), 2.49 (3 H, m, Ha-11, Hb-11, H-9), 2.38 (1 H, ddd, *J* = 12.9, 3.8, 2.2 Hz, Ha-7), 2.13 (1 H, td, *J* = 12.9, 4.9 Hz, Hb-7), 2.05–1.05 (28 H, m), 1.22 (1 H, dd, *J* = 12.7, 2.1 Hz, H-5), 0.90 (3 H, s, H-14), 0.82 (3 H, s, H-15), 0.71 (3 H, s, H-16). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.51 (s, C-12), 154.32 (s, C-23), 149.45 (s, C-8), 105.97 (t, C-13), 55.15 (d, C-5), 52.09 (d, C-9), 49.86 (d, C-17), 49.13(d, C-24), 42.04 (t, C-3), 39.09 (t, C-1), 39.02 (s, C-10), 37.68 (t, C-7), 33.56 (q, C-14), 33.50 (s, C-4), 32.80 (t, C-25 and C-29), 31.55 (t, C-11), 31.22 (t, C-22), 30.69 (t, C-18), 26.25 (t, C-19 and C-21), 25.48 (t, C-27), 25.40 (t, C-20), 24.73 (t, C-26 and C-28), 24.05 (t, C-6), 21.73 (q, C-15), 19.29 (t, C-2), 14.81 (q, C-16).

