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Phenethylamides With an Unusual 4-Oxo-2-oxolenyl Terpenoid Side Chain from *Glycosmis* Species

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Summary. Four new amides, glyparvin-A (**1**), dihydroglyparvin (**2**), khaochamide (**3**), and puhinamide (**4**) were isolated from the lipophilic leaf extracts of *Glycosmis* species collected in Thailand. Their structures were elucidated by spectroscopic methods. All amides have in common a phenethylamine moiety linked with a geranyloxy rest in *para*-position which is further transformed to an unusual terminal 4-oxo-2-oxolene five-membered ring, a non-lactonic dihydrofuranone. The different acid parts are derived either from 3-methylsulfonylpropenoic (**1**, **2**) or from isovaleric (**3**) and senecioic acid (**4**).

Keywords. Amides, sulfur containing; Dihydrofuranone; *Glycosmis*; *Rutaceae*; Sulfones.

Phenethylamide mit einer ungewöhnlichen terpenoiden 4-Oxo-2-oxolenyl-Seitenkette aus *Glycosmis*-Arten

Zusammenfassung. Aus den lipophilen Blattextrakten von thailändischen *Glycosmis*-Arten wurden vier neue Amide, Glyparvin-A (**1**), Dihydroglyparvin (**2**), Khaochamid (**3**) und Puhinamid (**4**) isoliert und ihre Struktur mit spektroskopischen Methoden aufgeklärt. Gemeinsames Merkmal aller vier Amide ist eine Phenethylamineinheit mit einer C10-terpenoiden Seitenkette in *para*-Position, wobei dieser Geranyloxyrest weiter zu einem terminalen 4-Oxo-2-oxolen-Fünfring (einem nicht-lactonischen Dihydrofuranon) transformiert ist. Die verschiedenen Säurekomponenten der Amide sind entweder 3-Methylsulfonylpropensäure (**1**, **2**) oder Isovalerian- (**3**) und Seneciosäure (**4**).

Introduction

The genus *Glycosmis* (*Rutaceae-Aurantioideae*) was shown to be a rich source of different amides characterized by sulfur-containing acid moieties [1–5]. In recent papers we have also reported on a series of novel anthranilic as well as isovaleric and senecioic acid derived amides from leaf extracts of different *Glycosmis* species

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[3, 5]. In order to get more information about the general biogenetic capacity of the genus we have now investigated the lipophilic leaf extracts of two different provenances of *Glycosmis parva* Craib. collected in eastern and southeastern Thailand as well as two collections from the northeastern province which may also be related to *G. parva* on the basis of morphological characters. *G. parva* itself mostly forms small shrublets characterized by simple, narrowly elliptic leaves and by a 3-celled ovary. It seems to be not uncommon in dry evergreen forests of Thailand [6].

Based on comparative HPLC-UV-diode array analyses of four different collections, the typical composition of the leaf extracts was shown to be characterized by new amides with an unusual terpenoid furanone-ring linked to a phenethylamine moiety. The present paper describes the isolation and structure elucidation of four new amides with a 4-oxo-2-oxolenyl terpenoid side chain which was only known so far from the coumarin geiparvarin isolated from *Geijera parviflora* Lindl. (*Rutaceae*) [7, 8]. Because of the significant *in vitro* activity of that particular coumarin against human nasopharynx carcinoma [9], special interest was focussed on the different molecular subunits, *i.e.* the furanone ring, the allyloxy group, and the coumarin moiety. Various replacements of these groups have shown that the furanone ring plays an important role in the antitumor activity [10]. In this connection, the present amides with the same furanone-allyloxy subunits are of special medicinal interest. Regarding the different acid moieties, the new amides fall into three groups: the compounds with methylsulfonylpropenoic acid designated as glyparvin-A (**1**) and dihydroglyparvin (**2**), and the compounds derived either from isovaleric or from senecioic acid named khaochamide (**3**) and puhinamide (**4**) with reference to the place of collections in Khao Chamao in southeast, and Phu Hin Rongkla in northeast Thailand.

Results and Discussion

The $CHCl_3$ fractions of the methanolic leaf extracts were treated as described in the Experimental to afford four compounds. The corresponding UV spectra are characterized by two maxima either at 290 and 220 nm in **1**, **3**, and **4** or at 260 and 220 nm in **2**. In the IR spectra, all compounds show the characteristic $>$N-H stretching band of secondary amides at 3253–3355 cm^{-1} and strong carbonyl bands at 1673–1696 cm^{-1} for the furanone ring and 1639–1656 cm^{-1} for the amide group. The sulfone group in **1** and **2** is indicated by two strong bands at 1130 and 1300 cm^{-1} (compare Ref. [2]).

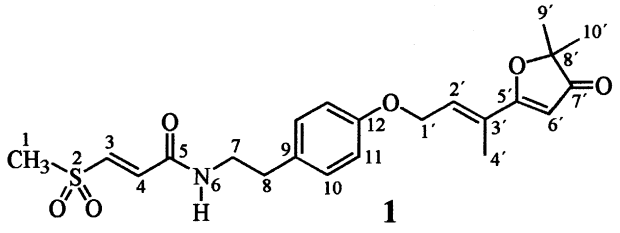
The ^{1}H NMR spectrum of glyparvin-A (**1**) (from *G. parva*, southeast Thailand) shows the typical aromatic resonance pattern for a *para*-substituted benzene (2×2H, compare Table 1). The chemical shifts at $\delta = 7.12$ and 6.88 ppm are characteristic for the *para*-oxygenated phenethylamides previously isolated from *G. angustifolia* [2]. The phenethyl resonances at $\delta = 3.61$ (dt, appearing as a ps q due to the coupling with the amide proton) and 2.82 (t) ppm together with the N-H signal at 5.92 (br t) ppm confirm this partial structure (compare Ref. [2], compounds **10**, **12**, and **14**). The acid component of amide **1** is (*E*)-3-(methylsulfonyl)-propenoic acid with the characteristic resonances at 7.36 (d, $J = 14.7$ Hz), 6.80 (d, $J = 14.7$ Hz), and 2.99 (s, S-Me) ppm [2]. The ^{13}C NMR data (see Exp.) for

these parts of the molecule agree also very well with Ref. [2]. The HR-MS molecular ion corresponding to $C_{22}H_{27}NO_6S$ leaves a rest of $C_{10}H_{13}O_3$ for a terpenoid geranyloxy derived side chain. The sequence $-O-CH_2-CH=C(CH_3)-$ follows clearly from the ^1H NMR data (t for 2H at $\delta = 4.75$ ppm, br t for 1H at 6.78 ppm, and a broadened methyl resonance at 2.00 ppm due to the usual terpenoid long range coupling between the olefinic CH and the methyl resonance). According to the ^1H NMR data, the remaining terminal sequence needs one olefinic CH ($\delta = 5.59$ ppm, s) and two identical methyl groups (6H at 1.40 ppm, sharp s). From the ^{13}C NMR spectrum one expects a ketonic C=O group ($\delta = 207.4$ ppm) and two further quaternary carbon atoms ($\delta = 183.3$ and 88.6 ppm). One additional oxygen atom completes the MS derived molecular formula. An oxygen containing five ring with a double bond, a ketonic oxo group, and two geminally attached methyl substituents fulfill these requirements. In contrast to the rather common lactonic C10 terpenoid side chains found in coumarin derivatives from other members of the *Rutaceae* family (*e.g.* furanocoumarin lactones like indicolactone from *Clausena anisata*) [11], the present five-ring is characterized by a separation of the ring oxygen and the carbonyl function to form a non-lactonic ring system. In the resulting 4-oxo-2-oxolene ring of compound **1**, the ^{13}C carbonyl resonance at $\delta = 207.4$ ppm is clearly in the ketone region, whereas the lactonic carbonyl in indicolactone is found at $\delta = 173.0$ ppm (ester region). Another clear difference in both isomeric ring systems is the presence of one methyl substituent at the lactone ring (the second terminal methyl group is oxidized to form the lactone by cyclization between C-9′ and C-6′), contrary to the two geminal methyl substituents in the 4-oxo-2-oxolene ring of **1** (cyclization C-8′ to C-5′). This rare terpenoid moiety has already been described as part of geiparvarin, a coumarin isolated from *Geijera* species [7, 9]. The ^1H NMR shift data of the cyclized geranyloxy side chain of **1** agree very well with the data of geiparvarin [12]. The ^{13}C NMR shifts of **1** are fully compatible with a 4-oxo-2-oxolenyl rest, the values for C-5′ ($\delta = 183.3$ ppm, enolic carbon), C-7′ (207.4, CO), C-8′ (88.6), and C-9′/10′ (23.1) compare very well with the corresponding data of a similar ring system described in Ref. [13] (a synthetic study directed towards pseurotins from *Pseudeurotium ovalis* Stolk, compound No. **17**). The (*E*) configuration of the terpenoid double bond was proved unambiguously by means of NOE, showing strong mutual effects between 1′-H and 4′-H (see Exp.). Further strong NOEs between 4′-H and 6′-H and a very weak effect from 6′-H to 2′-H are in favour of the highly preponderant conformation shown in the formula scheme, *s-cis* (or -*z*) for the C-3′–C-5′ single bond.

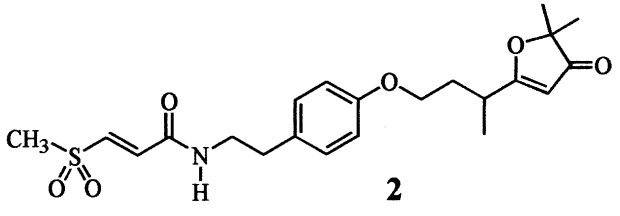
Compound **2** (from *G. parva*, east Thailand) is closely related to **1**, the only difference being the hydrogenated 2′-3′ double bond in the terpenoid side chain. This follows from MS, ^1H, and ^{13}C NMR data. In the sequence $-O-CH_2-CH_2-CH(CH_3)-$ with two diastereotopic methylene groups, all proton coupling constants could be evaluated (Table 1). It is interesting to note that in the ^1H NMR spectrum even the 9′ and 10′ methyl groups of the oxolene ring are slightly diastereotopic with a small but experimentally clearly detectable $\Delta\delta$ of 0.003 ppm. In comparison with compound **1**, the ^{13}C NMR spectrum of **2** does not show the olefinic resonances for C2′ (d) and C-3′ (s); however, two new signals appear at $\delta = 33.5$ (t, C-2′) and 32.6 (d, C-3′) ppm. Compound **2** is optically active

with an $[\alpha]_D$ of +51 (see Exp.). The same terpenoid side chain was also found in a coumarin derivative [8]. In derivatization of glyparvin (**1**), compound **2** was named dihydroglyparvin.

Khaochamide (**3**) (from *G. parva*, southeast Thailand, see Exp.) and puhinamide (**4**) (from *G. cf. parva*, northeast Thailand) are also related to glyparvin-A (**1**). The amino components are identical, but the acid moieties are different. Instead of the otherwise rare 3-methylsulfonylpropenoic acid, the rather common isovaleric or senecioic acids are incorporated in amides **3** and **4**, respectively. The sequence $-CO-CH_2-CH(CH_3)_2$ for **3** follows clearly from the characteristic ^1H NMR resonances at $\delta = 1.98$ (d for 2H), 2.06 (t of a heptet appearing as a ps-nonet), and a sharp d for 6H at 0.92 ppm. In the case of **4**, the acid moiety $-CO-CH=C(CH_3)_2$ is characterized by the olefinic resonance at $\delta = 5.48$ ppm (br s) and the two methyl groups at 2.14 and 1.82 ppm (two br s). A comparable pair of isovaleric and senecioic acid phenylethenylamides has been recently described for *G. crassifolia* (thalebanin-B and dehydrothalebanin-B) [5]. Another related (diacetyloxy-epoxy)-geranyloxy-phenethylamide of senecioic acid has been isolated from *Haplophyllum tuberculatum* (*Rutaceae*) from Saudi Arabia [14]. The high resolution mass spectra of **3** and **4** and the ^{13}C NMR spectrum of **4** confirm the proposed structures. According to HPLC analysis, puhinamide (**4**) was



1



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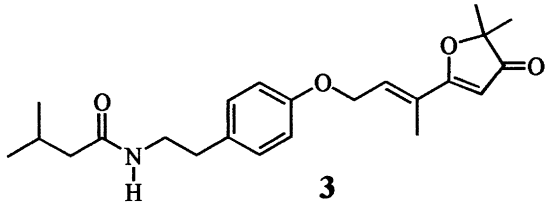

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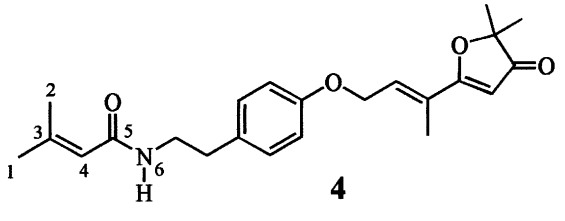

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Table 1. ^{1}H NMR data for compounds **1**–**4** (400 MHz, $CDCl_3$, *TMS*, δ (ppm))

	1	2	3	4	6	7	8	10[a]	11[a]
1	2.99 s	–	7.36 d	6.80 d	5.92 br.t	3.61 dt	2.82 t	7.12 dm	6.88 dm
2	2.99 s	–	7.37 d	6.82 d	6.08 br.t	3.60 dt	2.81 t	7.08 dm	6.82 dm
3	0.92 s	0.92 s	2.06 non	1.98 d	5.36 br.t	3.48 dt	2.76 t	7.13 dm	6.86 dm
4	1.82 s	2.14 s	–	5.48 br.s	5.33 br.t	3.52 dt	2.78 t	7.14 dm	6.87 dm

	1′	2′	3′	4′	6′	9′+10′
1	4.75 d	6.78 br.t	–	2.00 br.s	5.59 s	1.40 s
2	4.01 ddd[b] 3.98 ddd[b]	2.14 dddd[b] 2.00 dddd[b]	2.98 hex	1.30 d	5.29 s	1.37 2 × s[c]
3	4.75 d	6.78 br.t	–	1.99 br.s	5.59 s	1.40 s
4	4.75 d	6.79 br.t	–	1.99 br.s	5.59 s	1.40 s

Coupling constants: **1**: $J(3,4) = 14.7$ Hz, $J(6,7) = 6.0$ Hz, $J(7,8) = 6.9$ Hz, $J(10,11) = 8.5$ Hz, $J(1',2') = 5.9$ Hz; **2**: $J(3,4) = 14.7$ Hz, $J(6,7) = 6.0$ Hz, $J(7,8) = 6.8$ Hz, $J(10,11) = 8.6$ Hz, $J(1'a,1'b) = 9.6$ Hz, $J(1'a,2'a) = 5.9$ Hz, $J(1'a,2'b) = 5.8$ Hz, $J(1'b,2'a) = 5.6$ Hz, $J(1'b,2'b) = 7.0$ Hz, $J(2'a,2'b) = 14.0$ Hz, $J(2'a,3') = 7.3$ Hz, $J(2'b,3') = 6.8$ Hz, $J(3',4') = 7.0$ Hz; **3**: $J(1,3) = J(3,4) = 6.7$ Hz, $J(6,7) = 6.0$ Hz, $J(7,8) = 7.0$ Hz, $J(10,11) = 8.5$ Hz, $J(1',2') = 5.8$ Hz; **4**: $J(6,7) = 7.0$ Hz, $J(7,8) = 7.0$ Hz, $J(10,11) = 8.6$ Hz, $J(1',2') = 5.8$ Hz; [a] non-first order A_2B_2 system; [b] diastereotopic CH_2; [c] two diastereotopic s for $(CH_3)_2$: $\delta = 1.367$ and 1.370 ppm

also a major constituent of *G. cf. parva* from a second collection site in northeast Thailand (see Exp.).

Experimental

Melting points: Kofler hot stage microscope, Reichert (Vienna); NMR: Bruker AM 400 WB (*TMS*, δ (ppm) *J* in Hz); MS: Finnigan MAT 900 S; IR: Perkin-Elmer 398; Optical rotation: Perkin-Elmer 241 polarimeter; UV: Perkin-Elmer Lambda 5; HPLC: Hewlett-Packard HP 1090 II, UV diode array detection at 230 nm, column 290 × 4 mm (Spherisorb ODS, 5 µm), mobile phase MeOH (gradient 60–100%) in aqueous buffer (0.015 *M* phosphoric acid, 0.0015 *M* tetrabutylammonium hydroxide, $pH = 3$), flow rate 1 ml/min; all steps of the isolation procedure and the purity of the final products were examined by HPLC.

Plant material

G. parva Craib. (a) from Khao Chamao, Rayong, southeast Thailand, and (b) from Sakerat, Pak Thong Chai, Nakhon Ratchasima, east Thailand; *G. cf. parva* (c) from Phu Hin Rongkla, Phetchabun and (d) from Kaeng Sopha, Phitsanulok, both northeast Thailand. Voucher specimens are deposited at the Herbarium of the Institute of Botany, University of Vienna (WU).

Extraction and isolation

Collection (a): Dried leaves (25 g) were extracted with MeOH at room temperature for 7 days, filtered, and concentrated. The remaining aqueous phase was extracted with $CHCl_3$. The resulting extract was evaporated to dryness (750 mg) and roughly separated on a silica gel column (Merck silica gel 60, 35–70 mesh) by elution with hexane/ether mixture with ether increasing from 0 to 100% and finally with 0–40% methanol in ether. The combined fractions eluted with 10–25% MeOH in Et_2O (365 mg) were separated by preparative MPLC first with 50% EtOAc in hexane

(400 × 40 mm column, Merck LiChroprep silica 60, 25–40 µm, UV detection at 254 nm) to give 13 mg khaochamide (**3**) and further with 70% EtOAc in hexane to give 34 mg glyparvin-A (**1**). Collection (b): Dried leaves (50 g) were treated in the same way as described for (a). The final MPLC using 70% EtOAc in hexane afforded 25 mg dihydroglyparvin (**2**). Collection (c): Dried leaves (28 g) gave after MPLC with 50% EtOAc in hexane 53 mg puhinamide (**4**). Collection (d): HPLC analysis proved the presence of puhinamide (**4**) in the $CHCl_3$ fraction of the crude leaf extract. The purity of all isolated samples from collections (a), (b), and (c) was checked by HPLC in combination with diode array UV detection.

Glyparvin-A (**1**)

(*E*)-3-(Methylsulfonyl)-propenoic acid (*E*)-4-(3-(5,5-dimethyl-4-oxo-2-oxolen-2-yl)-2-butenyloxy)-phenethyl amide; colourless crystals from Et_2O; m.p.: 134–137°C; UV (MeOH): $\lambda_{max} = 288$, 239 sh, 226 nm; IR (KBr): $\nu_{max} = 3355$ m, 3061 w, 3015 w, 2974 w, 2926 w 1673 s, 1645 m, 1615 w, 1586 w, 1556 s, 1512 m, 1452 w, 1442 w, 1405 w, 1383 w, 1363 w, 1304 s, 1239 m, 1194 w, 1176 m, 1137 s, 1096 w, 1074 w, 1034 w, 991 w, 974 m, 961 w, 910 w, 868 w, 828 w, 796 m, 770 w, 642 w, 568 w, 513 m, 494 w cm^{-1}; ^1H NMR: see Table 1; differential NOEs: $1' \leftrightarrow 4', 1' \rightarrow 11, 4' \leftrightarrow 6', 6' \rightarrow 2'$ (v weak); ^{13}C NMR (62.9 MHz, $CDCl_3$, *TMS*): $\delta = 207.4$ (C-7′), 183.3 (C-5′), 161.5 (C-5), 157.2 (C-12), 139.0 (C-3), 135.4 (C-4), 132.0 (C-2′), 130.7 (C-9), 129.8 (C-10), 127.9 (C-3′), 114.9 (C-11), 100.0 (C-6′), 88.6 (C-8′), 64.8 (C-1′), 42.5 (C-1), 41.3 (C-7), 34.3 (C-8), 23.1 (9′ and 10′), 13.7 (C-4′) (assignments based on Refs. [2, 13]); MS (EI, 70 eV, 200°C): *m/z* (%) = 433 (12, M^+), 268 (100, M^+-geranyl side chain), 166 (56), 165 (97), 137 (38), 133 (15), 120 (96), 109 (47), 107 (55), 95 (21), 80 (76), 69 (100), 63 (58), 43 (42); HRMS: calcd. for $C_{22}H_{27}NO_6S$: 433.1559, found: 433.1560.

Dihydroglyparvin (**2**)

(*E*)-3-(Methylsulfonyl)-propenoic acid 4-(3-(5,5-dimethyl-4-oxo-2-oxolen-2-yl)-butyloxy)-phenethyl amide; colourless crystals from Et_2O; m.p: 93–94°C; $[\alpha]_D^{20} = +51$ ($CHCl_3$, $c = 0.2$), (578 nm) +55, (546) +61, (436) +112, (365) +194; UV (MeOH):$\lambda_{max} = 260$, 223 nm; IR (KBr): $\nu_{max} = 3295$ m 3079 w, 3025 w, 2979 w, 2927 w, 2883 w, 1696 s, 1656 s, 1633 m, 1596 s, 1555 m, 1516 m, 1480 w, 1462 w, 1407 w, 1383 w, 1363 w, 1327 w, 1305 s, 1255 m, 1194 w, 1176 m, 1133 s, 1089 w, 1038 w, 1010 w, 974 m, 941 w, 907 w, 866 w, 828 m, 805 w, 780 w, 764 w, 738 w, 666 w, 598 w, 554 w, 518 m, 491 w cm^{-1}; ^1H NMR: see Tab. 1; ^{13}C NMR (62.9 MHz, $CDCl_3$, *TMS*): $\delta = 161.5$ (C-5), 157.8 (C-12), 139.0 (C-3), 135.4 (C-4), 130.4 (C-9), 129.7 (C-10), 114.9 (C-11), 100.3 (C-6′), 88.5 (C-8′), 65.3 (C-1′), 42.5 (C-1), 41.4 (C-7), 34.3 (C-8), 33.5 (C-2′), 32.6 (C-3′), 22.8 (C-9′ and C-10′), 17.6 (C-4′); MS (EI, 70 eV, 180 °C): *m/z* (%) = 435 (7, M^+), 287 (19), 168 (61), 146 (18), 139 (100), 120 (20), 107 (25), 83 (39), 69 (43), 43 (80); HRMS: calcd. for $C_{22}H_{29}NO_6S$: 435.1716, found: 435.1718.

Khaochamide (**3**)

Isovaleric acid (*E*)-4-(3-(5,5-dimethyl-4-oxo-2-oxolen-2-yl)-2-butenyloxy)-phenethyl amide; colourless crystals from Et_2O; m.p.: 114–115°C; UV (MeOH): $\lambda_{max} = 291$, 241 sh, 227 nm; IR (CCl_4): $\nu_{max} = 3253$ w, 3073 w, 2956 w, 2932 w, 2870 w, 1693 s, 1646 m, 1634 m, 1563 s, 1511 m, 1453 w, 1401 w, 1377 w, 1360 w, 1302 w, 1245 m, 1198 w, 1177 m, 1126 w, 1093 w, 1072 w, 1042 w, 1026 w, 987 w, 952 w, 907 w, 863 w, 821 m, 803 w, 671 w, 616 w, 568 w, 530 w, 488 w cm^{-1}; ^1H NMR: see Tab. 1; MS (EI, 70 eV, 180°C): *m/z* (%) = 385 (8, M^+), 328 (4), 284 (22), 221 (64), 220 (100, M^+ – geranyl side chain), 166 (88), 165 (94), 151 (19), 137 (70), 136 (94), 123 (27), 120 (99), 109 (56), 107 (74), 102 (29), 96 (20), 95 (22), 91 (21), 85 (55), 79 (37), 77 (46), 69 (89), 57 (69), 43 (56); HRMS: calcd. for $C_{23}H_{31}NO_4$: 385.2253, found: 385.2250.

Puhinamide (**4**)

Senecioic acid (*E*)-4-(3-(5,5-dimethyl-4-oxo-2-oxolen-2-yl)-2-butenyloxy)-phenethyl amide; colourless crystals from Et_2O; m.p.: 88–90°C; UV (MeOH): $\lambda_{max} = 296$, 227 nm; IR (CCl_4): $\nu_{max} = 3326$ m, 3128 w, 3088 w, 3033 w, 2968 w, 2927 w, 2912 w, 2851 w, 1687 s, 1639 s, 1613 w, 1562 s, 1535 m, 1511 m, 1447 w, 1434 w, 1401 w, 1378 w, 1364 w, 1320 w, 1299 w, 1265 w, 1240 m, 1197 w, 1178 m, 1126 w, 1111 w, 1095 w, 1076 w, 1054 w, 1036 w, 957 w, 910 w, 860 w, 840 w, 816 m, 803 w, 744 w, 674 w, 654 w, 616 w, 588 w, 568 w, 533 w, 508 w cm^{-1}; ^1H NMR: see Tab. 1; ^{13}C NMR (62.9 MHz, $CDCl_3$, *TMS*) $\delta = 183.3$ (C-5′), 157.0 (C-12), 132.1 (C-2′), 129.9 (C-10), 127.9 (C-3′), 118.4 (C-4), 114.7 (C-11), 100.0 (C-6′), 88.6 (C-8′), 64.8 (C-1′), 40.4 (C-7), 34.9 (C-8), 27.1 (C-1), 23.1 (C-9′ and C-10′), 19.7 (C-2), 13.7 (C-4′), assignments based on Refs. [2, 5] and a ^{13}C data bank [15]; MS (EI, 70 eV, 140°C): *m/z* (%) = 383 (8, M^+), 300 (26), 284 (31), 219 (71, M^+ – geranyl side chain), 218 (97), 179 (32), 166 (88), 165 (94), 151 (23), 137 (63), 120 (81), 109 (71), 107 (70), 100 (77), 95 (31), 91 (41), 83 (86), 79 (67), 77 (79), 69 (100), 55 (90), 43 (82); HRMS: calcd. for $C_{23}H_{29}NO_4$: 383.2097, found: 383.2096.

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