Four New Alkaloids from *Consolida glandulosa*

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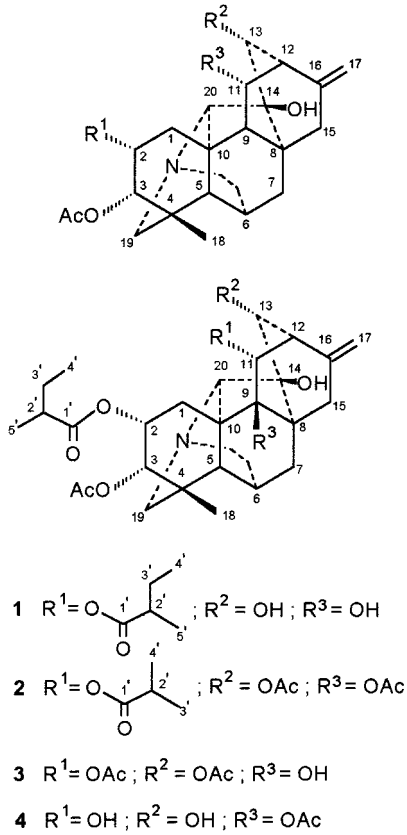
The structures of four new hetisine-type diterpenoids, 9-deoxyglanduline (**1**), glandulosine (**2**), 11,13-*O*-diacetylglanduline (**3**), and 9-*O*-acetylglanduline (**4**), isolated from *Consolida glandulosa*, were determined by two-dimensional NMR techniques. All the structures of these compounds were substantiated by a single-crystal X-ray analysis performed on compound **3**.

Diterpenoid alkaloids are mainly distributed in plants of the *Aconitum*, *Delphinium*, and *Consolida* genera and possess widely recognized pharmacological and biological activities.[1−4] In the recent past, our group has isolated an extensive number of diterpenoid alkaloids from these genera, yielding new alkaloids that have been submitted to chemical investigation[5−9] including their natural insecticidal activities.[10] In a previous work on *Consolida glandulosa* (Boiss. et Huet) Bornm. (Ranunculaceae) we reported on the isolation of the new diterpenoid alkaloids 11,13-*O*-diacetyl-9-deoxyglanduline, 13-*O*-acetyl-9-deoxyglanduline, 14-*O*-acetyl-9-deoxyglanduline, 13-*O*-acetylglanduline, and glanduline.[9] A further study of another harvest of this plant has now led to the isolation of four novel hetisine-type diterpenoid alkaloids, 9-deoxyglanduline (**1**), glandulosine (**2**), 11,13-*O*-diacetylglanduline (**3**), and 9-*O*-acetylglanduline (**4**).

Results and Discussion

The molecular formulas of the new alkaloids 9-deoxyglanduline (**1**, $C_{27}H_{37}NO_7$), glandulosine (**2**, $C_{30}H_{39}NO_9$), 11,13-*O*-diacetylglanduline (**3**, $C_{31}H_{41}NO_{10}$), and 9-*O*-acetylglanduline (**4**, $C_{29}H_{39}NO_9$) were derived from their HREIMS, ^{13}C NMR, and DEPT data. The NMR spectra of **1**−**4** (Table 1) show signals corresponding to highly functionalized hetisine-type diterpenoid alkaloids and are similar to those of the alkaloids previously isolated from this plant.[9] The ^1H NMR spectrum of **1** gave typical resonances for an angular methyl group at δ 1.04 s and for an exocyclic methylene at δ 4.71 br s and 4.90 br s, which are characteristic of this type of compounds, together with signals for protons linked to amine-carbons at δ 2.51 and 3.38 (each d, J = 12.5 Hz, AB system; δ 59.7 t, HMQC), at δ 3.15 (br s; δ 62.5 d, HMQC), and at δ 3.74 (s; δ 68.7 d, HMQC) that were tentatively assigned to H_2-19, H-6, and H-20, respectively. The identities of the H-6 and H-20 resonances were made obvious by the typical long-range *W* coupling that these protons showed in the $^1H-^1H$ COSY spectra, providing unequivocal proof of a hetisane skeleton for the new compound. Furthermore, signals observed downfield from δ 4.0 were attributed to geminal protons



belonging to alcohol or ester groups at δ 4.25 (d, J = 9.0 Hz; δ 75.8 d, HMQC) and 4.09 (t, J = 2.4 Hz; δ 79.9 d, HMQC) for two secondary alcohol groups, signals at δ 4.95 (d, J = 4.9 Hz; δ 170.4, HMBC) were assigned to a secondary acetate ester, and those at δ 5.42 (ddd, J = 4.4, 4.4, 2.5 Hz; δ 175.5 s, HMBC) to a secondary 2-methylbutyrate ester, thus accounting for six of the seven oxygen atoms in the molecule. The presence of the 2-methylbutyrate group was corroborated by the ions observed at *m*/*z* M^+ − 85, M^+ − 101, 85, and 57 in the EIMS spectrum.[11] Moreover, the seventh oxygen atom was in the form of a tertiary alcohol, as evidenced by the singlet signal at δ 79.7 observed in the ^{13}C NMR spectrum and from the molecular formula. Assuming a hetisane skeleton, the locations of these functional groups were determined by a mixed study of the 2D NMR, HMBC,[12] and $^1H-^1H$ COSY[13] experiments and DEPT data, starting from the unambiguous signals

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Table 1. ^{1}H and ^{13}C/HMQC NMR Data for Compounds **1**−**4** in $CDCl_3$ [a]

	1		**2**		**3**		**4**	
	proton	carbon	proton	carbon	proton	carbon	proton	carbon
1α	2.91 dd (15.8, 2.3)	31.4 t	2.85 dd (15.4, 2.5)	29.8 t	2.65 dd (14.9, 2.0)	26.8 t	2.95 dd (16.1, 2.4)	28.1 t
1*β*	2.05 dd (16.1, 4.3)	31.4 t	1.81 dd (15.4, 4.6)	29.8 t	1.83 dd (14.8, 4.6)	26.8 t	2.00 dd (16.0, 4.3)	28.1 t
2α	5.42 ddd (4.4, 4.4, 2.5)	67.7 d	5.47 ddd (4.6, 4.6, 2.5)	67.8 d	5.45 ddd (4.5, 4.5, 2.2)	68.0 d	5.35 ddd (4.3, 4.3, 2.8)	67.3 d
3*β*	4.95 d (4.9)	73.9 d	4.92 d (4.8)	73.8 d	4.88 d (4.8)	73.8 d	4.78 d (4.8)	72.7 d
4		42.2 s		42.2 s		41.9 s		40.1 s
5	1.80 s	61.5 d	1.80 s	61.0 d	2.62 s	55.6 d	2.76 s	53.7 d
6	3.15 br s ($W_{1/2}$ = 7)	62.5 d	3.13 br s ($W_{1/2}$ = 7)	62.5 d	3.05 br s ($W_{1/2}$ = 7)	61.9 d	3.49 br s ($W_{1/2}$ = 7)	63.0 d
7α	1.88 dd (13.9, 3.3)	31.7 t	1.90 dd (14.0, 3.4)	31.3 t	1.65 dd (14.0, 3.0)	26.3 t	1.83 dd (13.2, 2.9)	26.3 t
7*β*	1.41 dd (13.9, 2.2)	31.7 t	1.41 dd (14.1, 2.3)	31.3 t	1.82 dd (14.5, 2.3)	26.3 t	1.81 dd (14.2, 2.1)	26.3 t
8		44.2 s		44.8 s		47.7 s		46.3 s
9	2.00 d (9.3)	53.1 d	2.23 d (9.0)	51.3 d		80.3 s		80.2 s
10		46.0 s		45.6 s		50.7 s		50.5 s
11*β*	4.25 d (9.0)	75.8 d	5.11 d (8.9)	75.1 d	4.86 s	85.9 d	3.97 s	84.2 d
12	2.50 d (2.2)	52.4 d	2.68 d (2.8)	46.1 d	2.73 d (2.9)	45.4 d	2.38 br s ($W_{1/2}$ = 6)	50.5 d
13*β*	4.09 t (2.4)	79.9 d	5.02 dd (2.9, 1.7)	80.4 d	4.98 t (2.7)	79.6 d	3.91 t (2.0)	79.4 d
14		79.7 s		78.6 s		76.6 s		79.7 s
15α	2.01 m	30.8 t	2.21 d (16.3)	30.5 t	2.22 dt (17.8, 3.1)	28.0 t	1.87 br d (17.7)	27.5 t
15*β*	2.09 br d (17.8)	30.8 t	2.11 dt (17.9, 2.6)	30.5 t	2.03 br d (17.6)	28.0 t	2.04 dt (17.8, 2.6)	27.5 t
16		144.1 s		141.8 s		141.8 s		143.3 s
17-*E*	4.71 br s	108.5 t	4.83 br s	110.6 t	4.85 br s	110.6 t	4.64 br s	108.5 t
17-*Z*	4.90 br s	108.5 t	5.01 t (2.1)	110.6 t	5.02 br s	110.6 t	4.82 br s	108.5 t
18	1.04 s	25.6 q	1.03 s	25.4 q	1.03 s	25.6 q	1.05 s	25.2 q
19α	3.38 d (12.5)	59.7 t	3.34 d (12.5)	59.6 t	3.34 d (12.6)	60.1 t	3.59 d (12.5)	58.1 t
19*β*	2.51 d (12.4)	59.7 t	2.50 d (12.5)	59.6 t	2.50 d (12.6)	60.1 t	2.72 d (12.5)	58.1 t
20	3.74 s	68.7 d	3.56 s	69.2 d	3.55 s	67.9 d	4.15 s	68.7 d
1′		175.7 s		176.2 s		175.7 s		175.8 s
2′	2.40 sext (7.0)	41.8 d	2.59 sept (7.0)	34.4 d	2.36 sext (7.0)	41.4 d	2.36 sext (7.0)	41.3 d
3′ A	1.69 ddq (14.9, 7.5, 7.5)	26.7 t	1.18 d (6.8)	18.5 q	1.71 ddq (14.0, 7.0, 7.0)	26.1 t	1.59 ddq (14.0, 7.0, 7.0)	25.3 t
3′ B	1.49 ddq (13.8, 7.3, 7.3)	26.7 t			1.49 ddq (14.4, 7.2, 7.2)	26.1 t	1.40 ddq (14.0, 7.0, 7.0)	25.3 t
4′	0.92 t (7.4)	11.6 q	1.25 d (6.4)	19.7 q	0.92 t (7.4)	11.5 q	0.83 t (7.4)	11.2 q
5′	1.20 d (7.0)	17.1 q			1.25 d (7.0)	17.0 q	1.10 d (7.0)	16.6 q
AcO-3α	1.99 s	20.8 q	1.99 s	21.1 q	1.99 s	21.2 q	1.90 s	20.4 q
AcO-9α							1.88 s	23.1 q
AcO-11α			2.01 s	21.4 q	2.10 s	20.6 q		
AcO-13α			1.98 s	20.6 q	2.00 s	21.2 q		

[a] Chemical shifts in ppm relative to TMS; coupling constants (*J*) in Hz. ^{13}C NMR multiplicities were established by DEPT data.

belonging to the angular methyl group and the exocyclic methylene. Thus, the angular methyl resonance at *δ* 1.04 s showed long-range carbon−proton correlations with carbon signals at *δ* 73.9 d, 42.2 s, 61.5 d, and 59.7 t, which are assigned to C-3, C-4, C-5, and C-19, respectively; the corresponding linked protons were identified from the HMQC[14] data (see Table 1). The 2-methylbutyrate and acetate esters were located at C-2 and C-3, respectively, in view of the correlations observed between the one-proton resonance at *δ* 4.95 d for H-3 with the acetate carbonyl ester signal at *δ* 170.4 s in the HMBC experiment and with the one-proton signal at *δ* 5.42 ddd in the ^{1}H−^{1}H COSY spectrum. The multiplicity of the latter signal ascribed to H-2 as ddd (three coupling constants, one with H-3 and two with the methylene C-1 protons) excluded the possibility of functionalization at C-1. The subsequent HMBC or ^{1}H−^{1}H COSY correlations displayed by the signals for H_2-1, H-2, H-5, H-6, H-20, and H_2-17 allowed the assignment of the correct carbon and proton resonances for C-7, C-8, C-9, C-10, C-12, and C-15 (see Tables 2 and 3, Supporting Information) and indicated that C-7 (*δ* 31.7), C-9 (*δ* 53.1), C-12 (*δ* 52.4 d), and C-15 (*δ* 30.8 t) are not oxygenated. These findings allowed the location of the remaining oxygen functions at C-11, C-13, and C-14. Furthermore, from the scalar coupling displayed in the ^{1}H−^{1}H COSY between the H-12 signal with those at *δ* 4.09 and 4.25 for the corresponding alcohol geminal protons, we concluded that C-11 and C-13 bear a secondary hydroxyl each, compelling us to locate the tertiary alcohol at C-14 in compound **1**.

The stereochemistry of the secondary groups were deduced from the spatial relationships observed in the ROESY spectrum (see Table 4, Supporting Information) and from the multiplicity of the involved geminal protons in the rigid heptacyclic ring system. The H-3 proton must be in the *β*-axial orientation (ring A chair) in view of the observed spatial correlation with H-5 in the ROESY spectrum. The appearance of H-2 as a ddd, showing only typical axial−equatorial coupling (J = 4.4−2.2 Hz), requires this proton to be in the *β*-equatorial orientation. Finally, the long-range W coupling observed in the ^{1}H−^{1}H COSY spectrum between both alcohol geminal protons, H-13 and H-11, suggests they are in a *ψ*-axial (*β*) configuration, as were the alkaloids previously isolated from this plant.[6,9,15−17] The placement of the tertiary hydroxyl group at C-14 was further evidenced by the multiplicity of the H-13*β* signal, which is a triplet (J = 2.4 Hz), instead of a broad doublet that would be explained if there was a proton at C-14. The same reasoning used to assign the NMR signals of **1** was applied to compounds **2**−**4** (see Table 1 for NMR data). The similarities between the NMR spectra of **1** and those of glandulosine (**2**) suggested that the oxygen functions are located in both compounds in the same positions and stereochemistry. However, the NMR data (see Table 1) suggest that two acetate esters are present in compound **2** instead of the secondary alcohol groups in compound **1**. On the other hand, in compound **2** an isobutyrate ester group replaces the 2-methylbutyrate of compound **1**, which was evident from the ions at m/z M^+ −

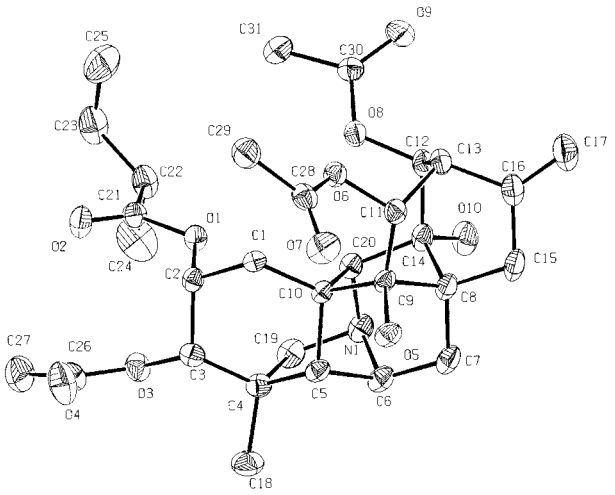

Figure 1. ORTEP drawing of compound **3**.

71, $M^+ - 87$, 71, and 87 in the EIMS spectrum.[11] It is not possible to draw analogous conclusions from the study of the NMR spectra of the new compounds 11,13-*O*-diacetylglanduline (**3**) and 9-*O*-acetylglanduline (**4**). Compounds **3** and **4** must bear an "extra" oxygen function at C-9. Thus, although the data for these compounds are very similar to those of **1** and **2**, the greatest change is in the mutiplicity of the signals for H-11, which are singlets instead of doublets. This assertion was supported by the singlet signals observed at δ 80.2 and 80.3 in the ^{13}C NMR spectra of **3** and **4**, which were absent in compounds **1** and **2**, assigned to each C-9 carbon (see Table 1). Compound **4** proved to have both a tertiary hydroxyl and an acetate ester. However, no conclusions derived from the HMBC data could be made about the exact location of the cited functions because of the very close chemical shift of their linked carbons. The placement of the tertiary acetate group at C-9 in compound **4** was determined from the spatial relationships encountered between the corresponding methyl acetate signal at δ 1.88 s with H-7β and H-15β (see Table 4, Supporting Information). To determine unambiguous structures for **1**−**4** and those of related compounds previously isolated from this plant, the molecular structure of **3**, except for the absolute configuration,[8] was confirmed by single-crystal X-ray diffraction analysis. The structure was solved by direct methods using SHELXS-86.[18] Refinement was performed with SHELXL-93[19] using full-matrix least squares with anisotropic thermal parameters for all non-H atoms. The hydrogen atoms were placed at idealized positions using the refinement program facilities and added to the final refinement as a fixed isotropic contribution. The refinement converged at R1 = 4.86% and wR2 = 12.98%, with a goodness of fit of 1.004 for 2732 reflections with $F_o > 4\sigma(F_o)$. The largest peak on the final difference map was 0.21 e/Å^3. The bond lengths and bond angles are within the usual ranges. There are two strong intermolecular hydrogen bonds involving the hydroxylic O5 and O10 as donors and the carboxylic O7 and the nitrogen atom as acceptors, the distances O5···O7 and O10···N being 2.85 and 2.69 Å, respectively, the angle O5−H5−O7 159.1°, and the O10−H10−N 133.0°. Figure 1 shows a computer-generated perspective of the final X-ray model of **3**.[20]

Experimental Section

General Experimental Procedures. Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. OR: Perkin-Elmer 241 polarimeter, 1 dm cell. IR spectra: Perkin-Elmer 1600 spectrophotometer. NMR spectra: Bruker AMX-500 and WP-200 SY spectrometers, solvent and TMS as internal standard. DEPT, ^{1}H COSY, HMQC, HMBC (J = 8 Hz), and ROESY (spin lock 500 ms) experiments were carried out with the pulse sequences given by Bruker. EIMS and exact mass measurements: Micromass Autospec instrument. Silica gel Merck Art. 7734 and Kieselgel 60 Merck Art. 5735 were used for column chromatography and preparative TLC, respectively. Spots on chromatograms were visualized with Dragendorff's reagent.

Plant Material. Plants were collected in Karapinar, 25 km beyond Malatya toward Gaziantep, Turkey, in the wilderness at an altitude of 1050 m, and authenticated by Professors J. Molero and C. Blanché, Botany Laboratory, Faculty of Pharmacy, University of Barcelona, where a voucher specimen, BCF 37770, has been deposited.

Extraction and Isolation. Aerial parts of plants were air-dried and ground (4.8 kg) and extracted with hexane. The residue was subsequently percolated exhaustively with 85% EtOH at room temperature. After removing the solvent under vacuum, the ethanolic extract (543 g) was treated with 0.1 M H_2SO_4 overnight and then filtered. The aqueous phase was progressively basified with 5% NaOH and extracted with CH_2Cl_2 to give a crude alkaloid material at pH 7 (Extr. N, 7.9 g) and at pH 12 (Extr. B, 12.9 g). The neutral extract was chromatographed over a silica gel column and eluted with mixtures of increasing polarity of hexane−EtOAc and AcOEt−MeOH. The fraction eluted with hexane−EtOAc (1:1) yielded the known compounds 13-*O*-acetylglanduline (85 mg) and 13-*O*-acetyl-9-deoxyglanduline (71 mg) together with the new alkaloids glandulosine (**2**) (10 mg) and 11,13-*O*-diacetylglanduline (**3**) (38 mg). Further elution with EtOAc−MeOH (98:2) yielded 9-deoxyglanduline (**1**) (18 mg), and with EtOAc−MeOH (90:10) 9-*O*-acetylglanduline (**4**) (72) mg. The new alkaloids were purified by fractional crystallization or preparative TLC. The identification of the known alkaloids were made by comparison with authentic samples.[9]

9-Deoxyglanduline (1): crystallized from hexane−EtOAc; mp 174−176 °C; $[\alpha]^{25}_D$ +6.6° (*c* 0.19, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3378, 3026, 2961, 2931, 1732, 1658, 1462, 1371, 1237, 1182, 1147, 1116, 1076, 1041, 984, 917, 900 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125.7 MHz), see Table 1; EIMS *m/z* 487 $[M]^+$ (27), 472 (5), 470 (9), 459 (20), 442 (12), 431 (56), 430 (57), 429 (25), 428 (84), 410 (7), 386 (5), 344 (12), 326 (10), 111 (14), 101 (3), 97 (24), 95 (21), 85 (19), 83 (35), 82 (21), 81 (25), 73 (25), 71 (35), 69 (49), 57 (100), 55 (72), 45 (43), 44 (85), 43 (70), 41 (70); HREIMS *m/z* 487.2575 (calcd for $C_{27}H_{37}O_7N$, 487.2570).

Glandulosine (2): amorphous solid; $[\alpha]^{25}_D$ +120° (*c* 0.1024, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3424, 3025, 2954, 2942, 1732, 1660, 1370, 1230, 1147, 1086, 1052, 1023, 980, 912 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 50.3 MHz), see Table 2 (Supporting Information); EIMS *m/z* 557 $[M]^+$ (2), 514 (3), 513 (3), 512 (14), 500 (6), 499 (20), 498 (72), 486 (7), 470 (2), 350 (6), 308 (14), 207 (7), 195 (7), 193 (7), 174 (12), 170 (8), 165 (10), 158 (7), 155 (8), 146 (10), 145 (13), 144 (28), 132 (11), 131 (11), 129 (11), 105 (16), 93 (13), 92 (15), 87 (5), 85 (15), 82 (14), 77 (13), 71 (81), 61 (13), 57 (100), 56 (19), 55 (22), 43 (20), 41 (24); HREIMS *m/z* 557.2644 (calcd for $C_{30}H_{39}O_9N$, 557.2624).

11,13-*O*-Diacetylglanduline (3): crystallized from hexane−EtOAc; mp 240−241 °C; $[\alpha]^{25}_D$ +60.4° (*c* 0.39, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3470, 3026, 2970, 2936, 1732, 1660, 1462, 1369, 1241, 1182, 1147, 1092, 1051, 1041, 978, 914 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 50.3 MHz), see Table 3 (Supporting Information); EIMS *m/z* 587 $[M]^+$ (4), 544 (4), 530 (8), 529 (41), 528 (100), 514 (2), 502 (1), 486 (1), 468 (2), 444 (4), 426 (2), 384 (2), 366 (2), 324 (2), 144 (3), 111 (2), 97 (3), 91 (2), 85 (4), 83 (3), 81 (2), 71 (6), 69 (5), 59 (20), 57 (24), 55 (5), 43 (14), 41 (1l); HREIMS *m/z* 587.2723 (calcd for $C_{31}H_{41}O_{10}N$, 587.2730).

9-*O*-Acetylglanduline (4): crystallized from hexane−EtOAc−MeOH; mp 147−150 °C; $[\alpha]^{25}_D$ +5.1° (*c* 0.14, EtOH); IR ν_{max} ($CHCl_3$) 3378, 3025, 2986, 2931, 1748, 1733, 1651, 1456, 1418, 1374, 1228, 1149, 1040, 981, 912 cm^{-1}; ^{1}H NMR ($CDCl_3$−CD_3OD, 4:1; 500 MHz) and ^{13}C NMR ($CDCl_3$−CD_3OD, 4:1; 50.3

MHz), see Table 4; EIMS *m/z* 503 $[M - Ac + H]^+$ (36), 498 (20), 486 (12), 475 (14), 474 (9), 458 (6), 446 (7), 445 (27), 444 (100), 428 (7), 360 (13), 342 (9), 144 (6), 111 (8), 101 (2), 97 (14), 95 (10), 85 (13), 83 (18), 81 (11), 73 (12), 71 (24), 69 (26), 67 (13), 60 (13), 59 (12), 57 (72), 55 (40), 45 (17), 43 (35), 41 (34); HREIMS $[M - Ac + H]^+$ *m/z* 503.2518 (calcd for $C_{27}H_{37}O_8N$, 503.2519).

Crystal Data for 3. Crystal data for compound **3**: $C_{31}H_{41}NO_{10}$, mol wt = 587.6, orthorhombic, space group *P*22121, $a = 8.189(2)$ Å, $b = 16.548(3)$ Å, $c = 21.909(5)$ Å, $V = 2968.9(11)$ Å^3, $Z = 4$, $D_c = 1.315$ g.cm^{-3}, $F(000) = 1256$, μ(Mo Kα) = 0.098 mm^{-1}. A single crystal of approximate dimensions 0.4 × 0.3 × 0.3 mm was used for all X-ray measurements. The intensity data of all unique reflections within the θ range 2.5−30° were collected at 273 K in an Enraf-Nonius CAD4 diffractometer, using Mo Kα radiation on a graphite monochromator. Three standard reflections monitored every 2 h of X-ray exposure showed no significant intensity variation. A total of 4804 unique reflections were recorded, of which 2732 with $F_o > 4\sigma(F_o)$ were taken into account for structure solution and refinements. The intensities were corrected for Lorentz and polarization factors, but no absorption correction was made. Crystallographic data of **3**, including atomic coordinates, have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 44-(0)1223-306033 or e-mail: deposit@ccdc.cam.ac.uk].

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Supporting Information Available: Tables 2−4 (HMBC, ^{1}H−^{1}H COSY, and ROESY data for compounds **1**−**4**) and tables of X-ray crystallographic data of compound **3**. This material is available free of charge via the Internet at http//pubs.acs.org.

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