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Antiinsectan Decaturin and Oxalicine Analogues from *Penicillium thiersii*

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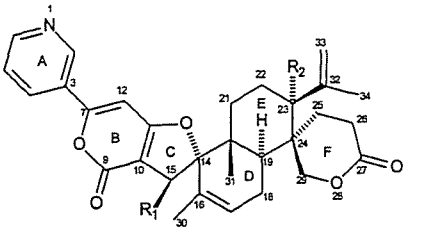
Three new oxalicine and decaturin analogues (**6**−**8**) have been isolated from organic extracts of *Penicillium thiersii*, along with the known compounds oxalicines A and B. These compounds (**4**−**8**) are members of a group of unique natural products containing terpenoid and pyridine moieties. The structures of the new compounds were elucidated by analysis of NMR and MS data. Most of these metabolites exhibit potent antiinsectan activity against the fall armyworm (*Spodoptera frugiperda*).

Our ongoing studies of fungicolous and mycoparasitic fungi[1−3] that attack and colonize sclerotia or stromata of wood decay fungi have afforded a variety of distinctive isolates of *Penicillium*, some of which are proving to be new species. Organic extracts from the fermented rice cultures of one such species, *Penicillium thiersii* (MYC-500 = NRRL 28147),[4] exhibited potent toxicity against *Spodoptera frugiperda* (fall armyworm) larvae in a dietary assay and were therefore subjected to chemical investigation. We have reported several novel metabolites from *P. thiersii*,[5−7] some of which possess potent antiinsectan activities.[5,7] One of these reports described the isolation of 15-deoxyoxalicine B (**1**) and decaturins A (**2**) and B (**3**), three new members of a rare skeletal class.[7] Compound **3** was produced by *P. thiersii*, while **1** and **2** were obtained from *Penicillium decaturense*, another new fungicolous *Penicillium* species. The only close known analogues of **1**−**3** that had been previously described were oxalicines A (**4**) and B (**5**).[8,9] However, **1**−**5** are biogenetically related to the pyripyropenes, a group of potent acyl-CoA cholesterol acyltransferase (ACAT) inhibitors from *Aspergillus fumigatus*.[10]

Continued work on extracts of *P. thiersii* has led to the isolation of oxalicines A (**4**) and B (**5**), as well as three additional new related compounds, 15-deoxyoxalicine A (**6**), decaturin C (**7**), and decaturin D (**8**). Details of the isolation, structure elucidation, and biological activities of these three new compounds are presented here, along with complete NMR spectral data for **4** and **5**, which have not been reported in the primary literature.



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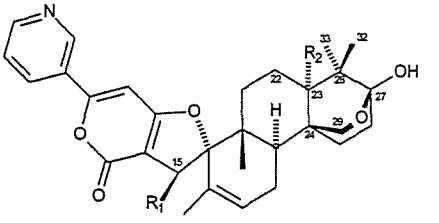
4 R_1 = OH R_2 = H
5 R_1 = OH R_2 = OH
6 R_1 = H R_2 = H



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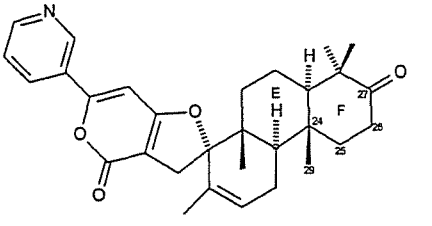
3 R_1 = OH R_2 = H
7 R_1 = H R_2 = H



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Results and Discussion

Bioassay-guided fractionation of the EtOAc extract of *P. thiersii* by column chromatography on Sephadex LH-20, followed by reversed-phase HPLC, afforded a number of new secondary metabolites. Aside from decaturin B (**3**), reported in an earlier communication,[7] five additional compounds possessing a 3-substituted pyridine moiety were also obtained (**4**−**8**). One characteristic feature of these compounds is their fluorescent behavior on TLC plates when viewed under a UV lamp (365 nm), which facilitated the isolation process.

EIMS and ^{13}C NMR analysis indicated that compound **4** possesses the molecular formula $C_{30}H_{33}NO_6$. A literature search led to its identification as oxalicine A.[8] This unique pyridine-containing compound was originally described as a metabolite of *Penicillium oxalicum*, and its structure was determined by X-ray crystallographic analysis. Although there was little doubt that **4** was oxalicine A, the reported ^1H NMR data were incomplete, and the ^{13}C NMR data differed slightly from those of our sample. Therefore, comprehensive 2D NMR analysis (COSY, HMQC, and HMBC) was performed, leading to the establishment of complete NMR assignments for oxalicine A (**4**) as shown in Table 1.

The molecular formula of compound **5** (oxalicine B) was found to contain one more oxygen atom than oxalicine A by analysis of ^{13}C NMR and HRESIMS data. The NMR data for **5** clearly indicated its structural resemblance to

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Table 1. NMR Data for Oxalicine A (**4**), Oxalicine B (**5**), and 15-Deoxyoxalicine A (**6**) in $CDCl_3$

	oxalicine A (**4**)		oxalicine B (**5**)		15-deoxyoxalicine A (**6**)	
position	^{13}C δ_C	^1H δ_H (mult., J in Hz)	^{13}C δ_C	^1H δ_H (mult., J in Hz)	^{13}C δ_C	^1H δ_H (mult., J in Hz)
2[a]	147.1	9.01 (d, 2)	147.1	9.01 (br s)	147.0	9.01 (br s)
3	127.3		127.3		127.5	
4	133.4	8.12 (ddd, 8.4, 2, 2)	133.4	8.10 (ddd, 8.4, 2, 2)	133.2	8.12 (br d, 8.4)
5	123.7	7.40 (dd, 8.4, 4.8)	123.7	7.40 (dd, 8.4, 4.8)	123.7	7.40 (dd, 8.4, 4.8)
6[a]	152.0	8.68 (dd, 4.8, 1.2)	151.9	8.69 (br d, 4.8)	151.6	8.67 (br s)
7	162.0		161.8		160.7	
9	170.5		170.7		170.0	
10	105.7		105.7		102.0	
11	160.2		160.3		160.4	
12	93.8	6.67 (s)	94.0	6.69 (s)	93.6	6.62 (s)
14	100.9		101.0		100.1	
15	74.2	5.50 (br s)	74.2	5.49 (s)	28.4	3.08 (d, 16); 2.96 (d, 16)
16	130.7		130.7		131.7	
17	130.2	5.79 (br d, 5.4)	129.9	5.79 (br d, 5)	127.7	5.72 (br d, 5.4)
18	24.8	2.32 (m)	24.5	2.42 (m)	24.6	2.27 (m)
		2.20 (br ddd, 18, 5, 5)		2.13 (ddd, 18, 5, 5)		
19	48.2	1.97 (dd, 12, 5)	43.6	2.63 (dd, 13, 5)	46.6	2.00 (dd, 11, 6)
20	42.1		41.0		41.3	
21	30.7[b]	2.63 (m)	24.5	2.32 (m)	30.6	1.56 (m)
		1.70 (m)		1.42 (ddd, 15, 4, 4)		
22	23.6	1.75 (m)	29.2	2.25 (ddd, 15, 15, 4)	23.4	1.77 (m)
		1.46 (m)		1.22 (br d, 15)		1.56 (m)
23	55.0	2.04 (br d, 12)	76.1		55.0	2.01 (br d, 13)
24	40.4		44.6		39.8	
25	30.6[b]	2.26 (ddd, 14, 10, 5)	26.0	2.50 (ddd, 14, 14, 5)	30.5	2.27 (m)
		1.73 (m)		1.60 (m)		1.77 (m)
26	29.8	2.43 (ddd, 16, 5, 5)	29.9	2.43 (m)	29.8	2.44 (ddd, 16, 6, 6)
		2.41 (ddd, 16, 10, 5)		2.32 (m)		2.40 (ddd, 16, 10, 5)
27	173.7		173.4		173.6	
29	67.6	4.55 (d, 12); 4.39 (d, 12)	67.8	4.49 (d, 13); 4.38 (d, 13)	67.4	4.53 (d, 12); 4.37 (d, 12)
30	19.4	1.58 (s)	19.4	1.58 (s)	18.4	1.70 (s)
31	16.1	1.30 (s)	15.9	1.28 (s)	16.0	0.95 (s)
32	146.0		150.7		145.7	
33	116.2	4.94 (s); 4.75 (s)	115.1	5.18 (s); 5.06 (s)	116.4	4.96 (s); 4.76 (s)
34	21.7	1.79 (s)	21.6	1.88 (s)	21.7	1.80 (s)

[a] The signals for H-2 and H-6 were broadened in some NMR samples. [b] These assignments may be interchanged.

oxalicine A. The main difference observed was the replacement of the C-23 methine (δ_C 55.0; δ_H 2.04) in **4** with a new oxygenated quaternary carbon (δ_C 76.1). This information strongly suggested that a new hydroxy group was attached to C-23 in compound **5**. Modest shifts of some nearby proton and carbon signals consistent with such a change were also observed. In previous work, 15-deoxyoxalicine B (**1**) had been isolated in our laboratory from another *Penicillium* sp. and its structure was independently solved by 2D NMR analysis.[7] The structure and relative stereochemistry of **5** was assigned by comparing the NMR data with those of oxalicine A (**4**) and 15-deoxyoxalicine B (**1**). Although compound **5** has not appeared previously in the primary literature, this metabolite was included and named oxalicine B in the Ph.D. thesis of R. P. Ubillas,[9] who coauthored the only prior literature report on oxalicine A.[8] Therefore, no detailed narrative spectral discussion of oxalicine B (**5**) is included here, but NMR spectral assignments were made in the current study, and these data are provided in Table 1.

With compounds **1**, **4**, and **5** in hand, the structure elucidation of compound **6** became straightforward. HRESIMS and ^{13}C NMR data revealed that **6** has the molecular formula $C_{30}H_{33}NO_5$, containing one oxygen atom less than that of oxalicine A (**4**). NMR data comparison indicated that compound **6** differed from **4** only in the presence of an isolated methylene unit at C-15 [δ_C 28.4, δ_H 3.08 (d, 16 Hz); 2.96 (d, 16 Hz)], rather than an oxygenated methine carbon as in **4** (δ_C 74.2, δ_H 5.50 s). Thus, compound **6** was identified as a new analogue of oxalicine A and was assigned the name 15-deoxyoxalicine A.

The NMR data for two additional metabolites, **7** and **8**, clearly showed the presence of the same pyridine-pyrone substructure as **1**–**6**, and thus were readily recognized as structural relatives. Comparison of the NMR and HRESIMS data for decaturin C (**7**) with those of decaturin B (**3**)[7] strongly suggested the absence of the C-15 hydroxy group as the only difference between the two, by analogy with the difference between 15-deoxyoxalicine A (**6**) and oxalicine A (**4**). Detailed analysis of COSY, NOESY, HMQC, and HMBC data for decaturin C confirmed this conclusion and allowed assignment of structure **7**. HMQC and HMBC data (Table 2) were particularly important in this instance due to overlap of several of the ^1H NMR signals in the upfield region. Analysis of the NOESY data for **7** was also complicated to some degree by overlap of key signals. However, the NMR data and NOESY correlations observed were consistent with retention of relative stereochemistry analogous to that reported for **2** and **3**, originally assigned on the basis of X-ray crystallographic analysis of **3**.[7] For example, NOESY correlations of one of the C-29 protons with signals for H_3-31, H_3-32, and one of the C-22 protons were fully consistent with the relative stereochemistry shown. Further support for the presence of the decaturin-type bridged-ring system was provided by observation of long-range (four-bond) *W*-type couplings of one of the C-29 protons with H-23 and of the other C-29 proton with one of the C-25 protons. Similar correlations were also observed in the data for decaturins A and B, but not for the oxalicines.

The molecular formula of compound **8** (decaturin D) was determined to be $C_{30}H_{35}NO_4$ (one oxygen atom less than

Table 2. NMR Data for Decaturins C (**7**) and D (**8**) in $CDCl_3$

	decaturin C (**7**)			decaturin D (**8**)	
position	^{13}C δ_C	^1H δ_H (mult., J in Hz)	HMBC (H → C)	^{13}C δ_C	^1H δ_H (mult., J in Hz)
2	146.9	9.00 (d, 2)	3, 4, 6, 7	147.0	9.01 (br s)
3	128.4			127.6	
4	133.3	8.12 (ddd, 7.8, 2, 2)	2, 6, 7	133.2	8.12 (ddd, 8.4, 2, 2)
5	123.7	7.40 (dd, 7.8, 4.8)	3, 4, 6	123.6	7.39 (dd, 8.4, 4.8)
6	151.5	8.68 (dd, 4.8, 1.2)	2, 4, 5	151.5	8.66 (br d, 4.8)
7	160.8			160.8	
9	170.1			170.1	
10	102.0			102.0	
11	160.2			160.2	
12	93.6	6.60 (s)	3, 7, 9, 10, 11	93.8	6.63 (s)
14	100.3			100.8	
15	28.2	3.08 (d, 16)	9, 10, 11, 14, 16, 20	28.4	3.10 (d, 16)
		2.92 (d, 16)	9, 10, 11, 14, 16, 20		2.95 (d, 16)
16	131.6			131.4	
17	127.6	5.69 (br d, 5.4)	14, 18, 19, 30	128.4	5.71 (br s)
18	23.3	2.14 (m)	16, 17, 19, 20	23.2	2.07 (m)
		1.80 (m)[a]	16, 17		
19	42.0	1.80 (m)[a]	14, 18, 20, 24, 31	46.9	1.76 (dd, 11, 6.0)
20	40.2[b]			40.9	
21	30.5	1.53 (m)	20, 23	31.7	1.57 (m)
		1.35 (m)	20, 31		1.45 (m)
22	19.0	1.55 (m)	21, 23, 24	19.0	1.53 (m)
23	49.9	1.29 (m)	22, 24, 28, 32, 33	54.6	1.42 (dd, 11, 4.2)
24	35.0			36.5	
25	34.4	2.16 (m)	23, 24, 26, 29	38.8	1.93 (ddd, 13, 7.8, 3.6)
		1.27 (m)	24, 26, 29		1.51 (m)
26	29.5	2.20 (m)	25, 27	34.0	2.55 (ddd, 16, 11, 7.8)
		1.73 (m)	25, 27		2.41 (ddd, 16, 7.2, 3.6)
27	98.0			217.0	
28	40.2[b]			47.3	
29	67.7	4.20 (dd, 9.0, 2.7)	23, 24	15.5	1.070 (s)
		3.88 (dd, 9.0, 1.8)	23, 24, 25, 27		
30	18.3	1.66 (br s)	14, 16, 17	18.5	1.68 (br d, 1.2)
31	15.8	0.87 (s)	14, 19, 20, 21	16.1	0.97 (s)
32	18.2	0.97 (s)	23, 27, 28, 33	21.4	1.04 (s)
33	27.2	1.02 (s)	23, 27, 28, 32	26.5	1.073 (s)

[a,b] Signals denoted by identical superscripts were essentially coincident. Thus, HMBC correlations observed for these signals were therefore difficult to establish with certainty, but were not required for assignment of the structure. Correlations observed for these δ-values are consistent with those expected for the structure, however, and proposed assignments for these correlations are included.

7) on the basis of EIMS and NMR data. The ^1H and ^{13}C NMR data for the A–E rings were essentially identical to those of **7**, suggesting that the difference resides in the eastern portion of the structure. In this case, the distinctive signals for the C-29 methylene protons observed in the spectrum of **7** (δ_H 3.88, 4.20; δ_C 67.7) were absent and were replaced by signals for a new isolated methyl group (δ_H 1.07, s; δ_C 15.5; H_3-29). In addition, a new ketone carbonyl signal was present (C-27, δ_C 217.0), replacing the doubly oxygenated quaternary carbon in **7**. Analysis of HMBC data established the structure of decaturin D as shown in **8**. For example, the signal for the new isolated methyl group (H_3-29) showed HMBC correlations with C-19, C-23, C-24, and C-25, requiring connection of both CH_3-29 and the isolated C-25–C-26 ethylene unit to quaternary carbon C-24. Both of the geminal methyl signals (H_3-32 and H_3-33) showed HMBC correlations with C-23, C-27, and C-28, leading to connection of the ketone carbon C-27 to quaternary carbon C-28. Correlations of both H_2-25 and H_2-26 to C-27 completed the new cyclohexanone ring subunit comprising the eastern portion (the F-ring) of decaturin D (**8**). All other HMBC correlations were fully consistent with the structure. The NMR data for the E–F fused-ring substructure assigned to **8** matched well with similar subunits in oleanene-type terpenoids, such as 11-deoxopulveric acid.[11] Although closely related to the other decaturins and to the oxalicines, structure **8** contains a previously unreported ring system. The relative stereochemistry of **8** was proposed to be analogous to that of decaturins B (**3**) and C (**7**).

Several attempts were made to assign the absolute stereochemistry of a representative member of this group of compounds (oxalicine A; **4**) by the application of Mosher's method and similar protocols, but degradation side-reactions prevailed and none of the desired acylation product was obtained. Thus, the absolute stereochemistry of oxalicines and decaturins remains unassigned.

The pyridinyl-α-pyrone substructure found in compounds **1**–**8** is rare among natural products. To our knowledge, the relatively simple plant metabolite anibine[12] and the pyripyropenes[10] are the only other precedents. The pyripyropenes are closely related to the oxalicines and decaturins from a biogenetic standpoint and are reportedly the most potent ACAT inhibitors known among natural products.[10] Like the pyripyropenes, the oxalicines and decaturins are clearly of mixed biogenetic origin and appear likely to arise from nicotinic acid, acetate, and terpenoid precursors,[13] with the oxalicines and decaturins incorporating a diterpenoid unit rather than the sesquiterpenoid component found in the pyripyropenes.

Oxalicine B (**5**), decaturin B (**3**), and decaturin D (**8**) showed potent antiinsectan activity[14] against *S. frugiperda*, causing 62%, 89%, and 77% reduction in growth rate (RGR), respectively, relative to controls when tested at a dietary level of 100 ppm. The known compound oxalicine

A (**4**) showed comparable activity. Since **4** is the most abundant component among its peers in this species, it was tested at a higher level (360 ppm), causing 98% RGR. Decaturin C (**7**) showed weaker activity in this assay, causing 28% RGR at 80 ppm, while 15-deoxyoxalicine A (**6**) was not tested due to sample limitations.

Experimental Section

General Experimental Procedures. General experimental procedures and details of the isolation, identification, and fermentation of *P. thiersii* (MYC-500 = NRRL 28147) have been described previously.[4,5] ^{1}H NMR data were obtained at 600 MHz (Bruker AMX-600) or 400 MHz (Bruker DRX-400), and ^{13}C NMR data were obtained at 100 MHz (DRX-400). COSY, HMQC, HMBC, and NOESY data were recorded at 600 MHz (^{1}H-dimension; AMX-600). NMR data were recorded in $CDCl_3$, and the chemical shifts were referenced to the residual solvent signals (δ_H 7.24/δ_C 77.0). Descriptions of MS, UV, and IR instrumentation and insect assay procedures employed have been published elsewhere.[14,15]

Extraction and Isolation. Solvent partition of the EtOAc extract of *P. thiersii* followed by Sephadex LH-20 column chromatography yielded 11 fractions.[5] The third fraction (71 mg) was further separated by reversed-phase HPLC (Alltech HS Hyperprep 100 BDS C_{18} column, 5 μm particles, 1.0 × 25 cm; flow rate 2.0 mL/min; 60% to 100% CH_3CN in H_2O over 40 min) to yield 15-deoxyoxalicine A (**6**, 1.5 mg, t_R 14.2 min) and decaturin D (**8**, 2.7 mg, t_R 23 min). The seventh fraction (231 mg) from the LH-20 column, eluted with 1:4 hexane–CH_2Cl_2, was further separated on a silica gel column. The sixth fraction (30 mg), eluted with 100% EtOAc, was further separated by reversed-phase HPLC (same column conditions as above, except using 60% CH_3CN in H_2O over 20 min) to yield oxalicine A (**4**, 9.6 mg, t_R 11.1 min) and decaturin C (**7**, 4.6 mg, t_R 12.8 min). The eleventh fraction (83 mg) from the LH-20 column was subjected to HPLC (same column conditions as above, except using 50% to 70% CH_3CN in H_2O over 20 min) to yield oxalicine B (**5**, 3.2 mg, t_R 9.3 min) and decaturin B (**3**, 6.5 mg, t_R 10.8 min).

Oxalicine A (4): colorless crystals, mp 189–194 °C (lit. 193–198 °C); $[\alpha]_D$ +142° (*c* 0.3, CH_2Cl_2); ^{1}H and ^{13}C NMR data, see Table 1; HMBC (H# → C#) H-2 → C-3, C-4, C-6; H-4 → C-2, C-6, C-7; H-5 → C-3, C-6; H-6 → C-2, C-4, C-5; H-12 → C-3, C-7, C-9, C-10; H-15 → C-9, C-10, C-16; H-17 → C-14, C-18, C-19, C-30; H-19 → C-18, C-20, C-21/25, C-24, C-29, C-31; H-21a → C-19, C-20, C-23, C-31; H-22b → C-20, C-24; H-23 → C-22, C-24, C-29, C-34; H-25a → C-23, C-24, C-26, C-27; H_2-26 → C-24, C-25, C-27; H_2-29 → C-19, C-23, C-24, C-25, C-27; H_3-30 → C-14, C-16, C-17; H_3-31 → C-14, C-19, C-20, C-21; H_2-33 → C-23, C-34; H_3-34 → C-23, C-32, C-33; EIMS (70 eV) obsd *m/z* 503 (M^+, rel int 26), 488 (4), 485 (13), 216 (24), 202 (20), 173 (46), 148 (68), 119 (35), 106 (48); UV, IR, and X-ray crystallographic data have been previously reported.[8]

Oxalicine B (5): colorless crystals, mp 143–146 °C; $[\alpha]_D$ +92° (*c* 0.1, CH_2Cl_2); UV (MeOH) λ_{max} 232 (ϵ 17 400), 271 (ϵ 6400), 317 (ϵ 4000); IR (CH_2Cl_2) 3436, 2973, 2932, 2846, 1733, 1639, 1573 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS (70 eV) obsd *m/z* 519 (M^+, rel int 11), 501 (42), 488 (18), 404 (16), 216 (25), 202 (34), 177 (58), 148 (84), 119 (26), 106 (100); HRESIMS obsd $(M + H)^+$ at *m/z* 520.2338, calcd for $C_{30}H_{34}NO_7$, 520.2335.

15-Deoxyoxalicine A (6): colorless oil; $[\alpha]_D$ +54° (*c* 0.1, CH_2Cl_2); UV (MeOH) λ_{max} 229 (ϵ 10 200), 271 (ϵ 3900), 316 (ϵ 2200); ^{1}H and ^{13}C NMR data, see Table 1; EIMS (70 eV) obsd *m/z* 487 (M^+, rel int 42), 472 (100), 267 (12), 252 (35), 228 (12), 202 (75), 148 (12), 106 (26); HRESIMS obsd $(M + H)^+$ at *m/z* 488.2446, calcd for $C_{30}H_{34}NO_5$, 488.2437.

Decaturin C (7): colorless crystals, mp 171–174 °C; $[\alpha]_D$ +167° (*c* 0.2, CH_2Cl_2); UV (MeOH) λ_{max} 235 (ϵ 15 000), 270 (ϵ 5900), 325 (ϵ 1600); IR (CH_2Cl_2) λ_{max} 3412, 2964, 2878, 1721, 1636, 1587 cm^{-1}; ^{1}H, ^{13}C NMR, and HMBC data, see Table 2; EIMS (70 eV) obsd *m/z* 489 (M^+, rel int. 39), 474 (10), 228 (10), 202 (66), 148 (68), 106 (100); HRESIMS obsd $(M + H)^+$ at *m/z* 490.2600, calcd for $C_{30}H_{36}NO_5$, 490.2593.

Decaturin D (8): colorless oil; $[\alpha]_D$ +58° (*c* 0.1, CH_2Cl_2); UV (MeOH) λ_{max} 233 (ϵ 14 000), 270 (ϵ 5100), 327 (ϵ 3100); IR (CH_2Cl_2) 3379, 2944, 2867, 1727, 1705, 1634, 1576 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; selected HMBC data ($CDCl_3$) H_2-25 → C-24, 26, 27; H_2-26 → C-24, 25, 27; H_3-29 → C-19, 23, 24, 25; H_3-32 → C-23, 27, 28, 33; H_3-33 → C-23, 27, 28, 32; EIMS (70 eV) obsd *m/z* 473 (M^+, rel int 56), 458 (80), 267 (11), 253 (38), 228 (35), 202 (100), 148 (26), 119 (36), 106 (29); HRESIMS obsd $(M + H)^+$ at *m/z* 474.2651, calcd for $C_{30}H_{36}NO_4$, 474.2644.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **4**–**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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