

Lactimidomycin, Iso-migrastatin and Related Glutarimide-containing 12-membered Macrolides are Extremely Potent Inhibitors of Cell Migration

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General Experimental Procedures. Optical rotations were measured in CHCl₃ on a Perkin-Elmer 241 instrument at the sodium D line (589 nm). Electrospray mass spectra data were obtained on an Agilent 1100 HPLC-MSD SL quadrupole mass spectrometer equipped with both orthogonal pneumatically assisted electrospray and atmospheric pressure chemical ionization sources. High-resolution mass spectral analyses were acquired on an IonSpec HiResMALDI FT-Mass spectrometer. ¹H and ¹³C NMR spectra were recorded at 25°C on Varian Unity Inova 400MHz or 500MHz instruments. ¹H and ¹³C NMR chemical shifts were referenced to residual solvent signals: δ_H 7.27 and δ_C 77.23 for CDCl₃. ¹H-¹H COSY, HMQC (*J*_{CH}=140 Hz), and gHMBC (ⁿ*J*_{XH}=8.0 Hz) were performed using standard VARIAN pulse sequences.

Fractions obtained during isolation, reaction mixture and compounds finally purified were monitored by either analytical HPLC or TLC on E. Merck silica gel-60F plates using CHCl₃-MeOH (9:1) or EtOAc-Hexane (7:3) as developing solvents and iodine as the visualizing agent. The mobile phase used for HPLC was comprised of buffer A (15% CH₃CN in H₂O containing 0.1% HOAc) and buffer B (80% CH₃CN in H₂O containing 0.1% HOAc). Analytical HPLC was performed using a Prodigy ODS-2 column (150 × 4.6 mm, 5μm) eluted with a linear gradient of 0% to 80% buffer B over 20 min, followed by 5 min at 80% buffer B at a flow rate of 1.0 mL/min with UV detection at 205 nm.

Silica gel (Natland International Corporation, 230-400 mesh size) was used for column chromatography. Chemical reagents were purchased from Sigma and used without further purification.

Acquisition of precursors for 2, 3-olefin reduction via either Stryker's reagent or thiol addition. Compounds **5**, **9-12**, and **14** were produced and purified from *Streptomyces platensis* NRRL18993.¹ Also isolated from this strain were the precursors to reduced congeners **25** and **26**. These precursors are noted as **25a** (17-hydroxy-8-desmethoxy-isomigrastatin) and **26a** (16, 17-didehydro-8-desmethyl-isomigrastatin), respectively.¹ Compounds **7** and **13** were produced and purified from *Streptomyces amphibiosporus*.² From this strain was also isolated the precursor to compound **27** hereafter referred to as **27a** (9α-hydroxy-8, 9-dihydro-lactimidomycin). Compounds **15** and **16** were isolated from recombinant *S. amphibiosporus*, the details of which will be published elsewhere. Cysteine conjugates **28** and **29** have been previously reported.¹

Semisynthesis of compounds 6, 8, and 17-27 using Stryker's reagent. The C2/C3 double bond of the α, β-unsaturated ester group was regioselectively reduced by Stryker's reagent [(Ph₃P)CuH]₆.³ A general procedure for production of 6, 8, and 17-27 from their corresponding unsaturated precursors by Stryker's reagent is shown below:

To a solution of substrate (A mg, mmol) in water-saturated benzene (B mL, deoxygenated with argon for 10 min), was added C mg, mmol [(Ph₃P)CuH]₆. The mixture was stirred at room temperature under an atmosphere of argon and progress of reactions monitored by HPLC. After D hrs, reactions were quenched by exposure to air for 1h. Reaction mixtures were concentrated to dryness, re-dissolved in MeOH, centrifuged to remove the precipitates, and again evaporated to dryness. The resulting residues were purified by repeated silica gel flash column chromatography using CHCl₃-MeOH (10:0-95:5) and Hexane-EtOAc (4:6~10:0) to give purified products (E mg).

HPLC analysis of C2/C3 reduced compounds **6**, **8**, and **17-27** were found to be stable and unchanged following incubation in H₂O at 37°C for 12 hrs.

Substrate (A mg, mmol)	Benzene (B ml)	[(Ph ₃ P)CuH] ₆ (C mg, mmol)	Reaction time (D hrs)	Product (E mg, mmol)
5 (35.0 mg, 0.710 mmol)	25	75.0 mg, 0.380 mmol	2	6 (22.1 mg, 0.045 mmol)
7 (170.0 mg, 0.371 mmol)	50	400.0 mg, 0.204 mmol	12	8 (75.2 mg, 0.164 mmol)
9 (224.0 mg, 0.459 mmol)	20	331.0 mg, 0.169 mmol	2	17 (31.0 mg, 0.063 mmol)
10 (68.2 mg, 0.148 mmol)	6	107.0 mg, 0.055 mmol	2	18 (41.8 mg, 0.090 mmol)
11 (339.0 mg, 0.741 mmol)	30	533.0 mg, 0.271 mmol	2	19 (54.0 mg, 0.117 mmol)

12 (67.4 mg, 0.133 mmol)	6	98.0 mg, 0.050 mmol	2	20 (12.6 mg, 0.025 mmol)
13 (68.0 mg, 0.148 mmol)	25	140.0 mg, 0.071 mmol	6	21 (42.0 mg, 0.091 mmol)
14 (73.4 mg, 0.154 mmol)	6	112.0 mg, 0.057 mmol	2	22 (38.6 mg, 0.081 mmol)
15 (40.0 mg, 0.082 mmol)	25	110.0 mg, 0.056 mmol	12	23 (8.6 mg, 0.017 mmol)
16 (20.0 mg, 0.042 mmol)	25	55.0 mg, 0.028 mmol	6	24 (3.0 mg, 0.006 mmol)
25a (71.0 mg, 0.149 mmol)	6	110.0 mg, 0.056 mmol	2	25 (37.0 mg, 0.077 mmol)
26a (540.0 mg, 1.14 mmol)	15	820.0 mg, 0.418 mmol	2	26 (105.1 mg, 0.221 mmol)
27a (67.8 mg, 0.142 mmol)	15	75.0 mg, 0.038 mmol	3	27 (15.6 mg, 0.033 mmol)

Physico-chemical properties of compounds **6**, **8**, and **17-27**.

2, 3-dihydro-isomigrastatin (**6**). Colorless oil; $[\alpha]_D^{25} +140.0^\circ$ (*c*, 0.50, CHCl₃); ¹H NMR, see Table S1; ¹³C NMR, see Table S4; HR(+)-MALDI-MS *m/z* 514.2799 [(M+Na)⁺], calcd for [C₂₇H₄₁O₇N Na]⁺ 514.2775.

2, 3-dihydro-lactimidomycin (**8**). Colorless oil; $[\alpha]_D^{25} +102.4^\circ$ (*c*, 0.25, CHCl₃); ¹H NMR, see Table S1; ¹³C NMR, see Table S4; HR(+)-MALDI-MS *m/z* 482.2528 [(M+Na)⁺], calcd for [C₂₆H₃₇O₆N Na]⁺ 482.2513.

2, 3-dihydro-16, 17-didehydro-isomigrastatin (**17**). Colorless oil; $[\alpha]_D^{25} +218.5^\circ$ (*c*, 0.14, CHCl₃); ¹H NMR, see Table S1; ¹³C NMR, see Table S4; HR(+)-MALDI-MS *m/z* 512.2634 [(M+Na)⁺], calcd for [C₂₇H₃₉O₇N Na]⁺ 512.2619.

2, 3-dihydro-8-desmethoxy-isomigrastatin (**18**). Colorless oil; $[\alpha]_D^{25} +105.2^\circ$ (*c*, 0.12, CHCl₃); ¹H NMR, see Table S1; ¹³C NMR, see Table S4; HR(+)-MALDI-MS *m/z* 484.2692 [(M+Na)⁺], calcd for [C₂₆H₃₉O₆N Na]⁺ 484.2670.

2, 3-dihydro-16, 17-didehydro-8-desmethoxy-isomigrastatin (**19**). Colorless oil; $[\alpha]_D^{25} +212.7^\circ$ (*c*, 0.092, CHCl₃); ¹H NMR, see Table S2; ¹³C NMR, see Table S4; HR(+)-MALDI-MS *m/z* 482.2522 [(M+Na)⁺], calcd for [C₂₆H₃₇O₆N Na]⁺ 482.2513.

2, 3-dihydro-17-hydroxy-isomigrastatin (**20**). Colorless oil; $[\alpha]_D^{25} +162.1^\circ$ (*c*, 0.05, CHCl₃); ¹H NMR, see Table S2; HR(+)-MALDI-MS *m/z* 530.2738 [(M+Na)⁺], calcd for [C₂₇H₄₁O₈N Na]⁺ 530.2724.

2, 3, 8, 9-tetrahydro-lactimidomycin (**21**). Colorless oil; $[\alpha]_D^{25} +141.3^\circ$ (*c*, 0.075, CHCl₃); ¹H NMR, see Table S3; ¹³C NMR, see Table S5; HR(+)-MALDI-MS *m/z* 484.2691 [(M+Na)⁺], calcd for [C₂₆H₃₉O₆N Na]⁺ 484.2670.

2, 3-dihydro-8-desmethyl-isomigrastatin (**22**). Colorless oil; $[\alpha]_D^{25} +147.1^\circ$ (*c*, 0.49, CHCl₃); ¹H NMR, see Table S2; ¹³C NMR, see Table S4; HR(+)-MALDI-MS *m/z* 500.2631 [(M+Na)⁺], calcd for [C₂₆H₃₉O₆N Na]⁺ 500.2619.

2, 3-dihydro-9β-methoxy-8, 9-dihydro-lactimidomycin (**23**). Colorless oil; $[\alpha]_D^{25} +90.5^\circ$ (*c*, 0.092, CHCl₃); ¹H NMR, see Table S3; ¹³C NMR, see Table S5; HR(+)-MALDI-MS *m/z* 514.2795 [(M+Na)⁺], calcd for [C₂₇H₄₁O₇N Na]⁺ 514.2775.

2, 3-dihydro-9β-hydroxy-8, 9-dihydro-lactimidomycin (**24**). Colorless oil; $[\alpha]_D^{25} +108.2^\circ$ (*c*, 0.059, CHCl₃); ¹H NMR, see Table S3; ¹³C NMR, see Table S5; HR(+)-MALDI-MS *m/z* 500.2625 [(M+Na)⁺], calcd for [C₂₆H₃₉O₇N Na]⁺ 500.2619.

2, 3-dihydro-17-hydroxy-8-desmethoxy-isomigrastatin (**25**). Colorless oil; $[\alpha]_D^{25} +109.9^\circ$ (*c*, 0.14, CHCl₃); ¹H NMR, see Table S2; ¹³C NMR, see Table S5; HR(+)-MALDI-MS *m/z* 500.2631 [(M+Na)⁺], calcd for [C₂₆H₃₉O₇N Na]⁺ 500.2619.

2, 3-dihydro-16, 17-didehydro-8-desmethoxy-isomigrastatin (**26**). Colorless oil; $[\alpha]_D^{25} +120.0^\circ$ (*c*, 0.27, CHCl₃); ¹H NMR, see Table S3; ¹³C NMR, see Table S5; HR(+)-MALDI-MS *m/z* 498.2487 [(M+Na)⁺], calcd for [C₂₆H₃₇O₇N Na]⁺ 498.2462.

2, 3-dihydro-9 α -hydroxy-8, 9-dihydro-lactimidomycin (**27**). Colorless oil; $[\alpha]_D^{25} +85.7^\circ$ (*c*, 0.099, CHCl₃); ¹H NMR, see Table S3; ¹³C NMR, see Table S5; HR(+)-MALDI-MS *m/z* 500.2635 [(M+Na)⁺], calcd for [C₂₆H₃₉O₇N Na]⁺ 500.2619.

References:

1. Ju, J.; Lim, S.-K.; Jiang, H.; Seo, J.-W.; Shen, B. *J. Am. Chem. Soc.*, **2005**, *127*, 11930-11931.
2. Ju, J.; Seo, J. -W.; Her, Y.; Lim, S. -K.; Shen, B. *Org. Lett.* **2007**, *9*, 5183-5186.
3. Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291-293.

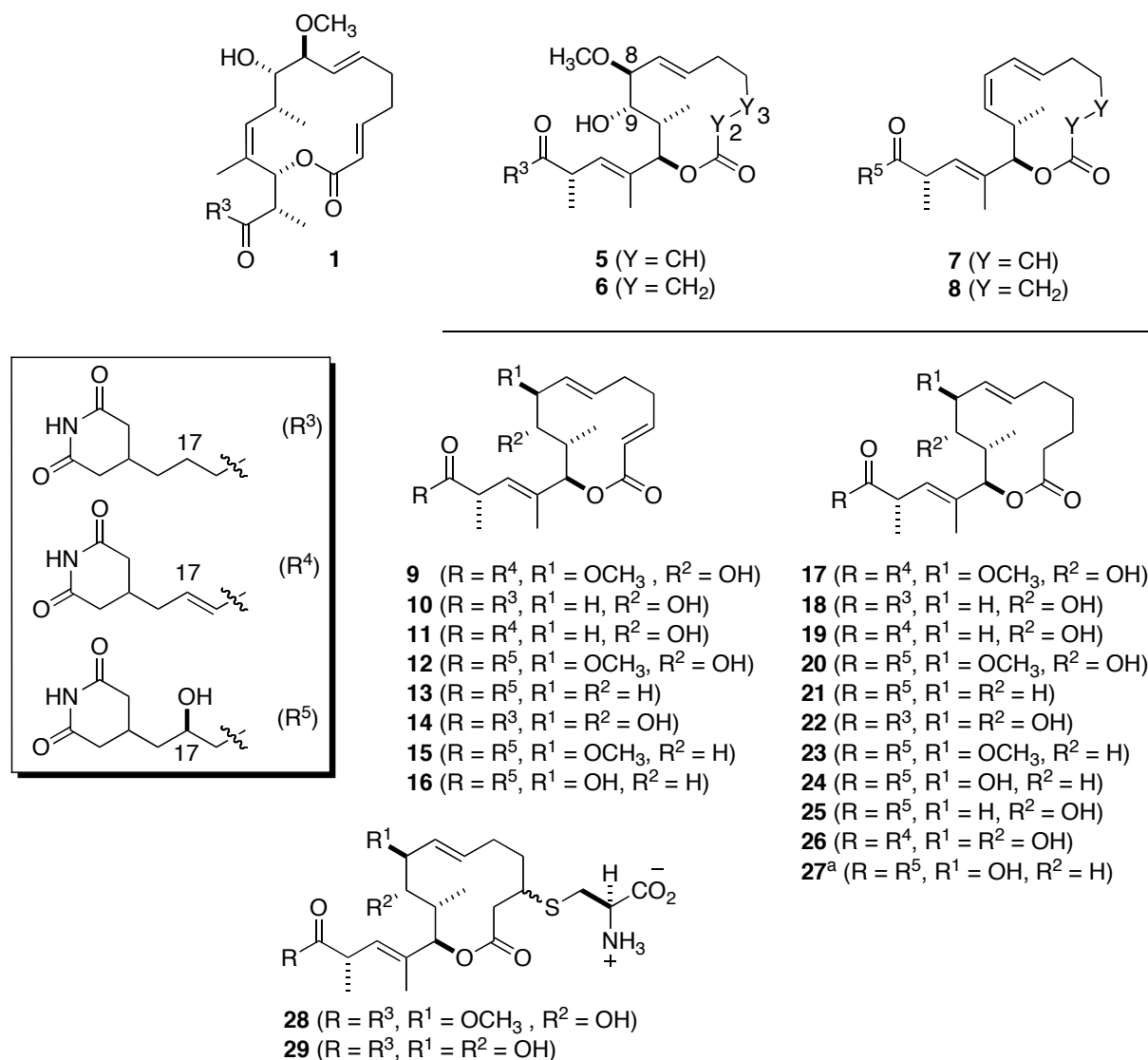


Figure S1. Structures of the natural products migrastatin (**1**), iso-migrastatin (**5**) and lactimidomycin (**7**) and their natural congeners (**9-16**) and semi-synthetic analogs (**6**, **8**, and **17-29**) subjected to SWH assays *en route* to evaluation as cell migration inhibitors in this study. ^aCompound **27** is the 8-(*S*)-epimer of compound **24**.

Table S1. ¹H NMR (500MHz for **6** and **8**, 400MHz for **17** and **18**) spectral data of compounds **6**, **8**, **17** and **18** in CDCl₃

Position	6 ^a	8 ^a	17 ^a	18 ^a
2	2.10, m; 2.38, m	2.35, 2H, m	2.16, m; 2.44, m	2.16, m; 2.34, m
3	1.70, 2H, m	1.56, m; 2.00, m	1.30, m; 1.72, m	1.55, 2H, m
4	1.72, 2H, m	1.56, m; 1.84, m	1.75, 2H, m	1.78, 2H, m
5	2.02, 2H, m	2.00, m; 2.34, m	1.92, m; 2.20, m	2.04, 2H, m
6	5.68, dt (16.0, 7.0)	5.73, dt (15.5, 5.0)	5.69, 1H, dt (16.0, 7.6)	5.44 m, overlap
7	5.14, dd (10.0, 7.0)	6.18, m	5.29, 1H, dd (16.0, 6.8)	5.44 m, overlap
8	3.29, dd (9.0, 7.0)	6.11, m	3.55, 1H, m	2.15 m; 2.24 m
9	3.65, 1H, dd (9.0, 2.5)	5.00, t (11.0)	3.67, 1H, dd (9.2, 2.4)	3.75, 1H, m
10	1.90 m	3.36 m	1.90, 1H, m	1.85 m
11	5.03 d (3.5)	5.11, d (5.0)	5.04, 1H, d (3.2)	5.07 m (overlap)
13	5.13 d (9.5)	5.24, d (9.5)	5.15, 1H, d (10.0)	5.05 m (overlap)
14	3.40 m	3.36 m	3.54, 1H, m	3.37 m
16	2.40 m; 2.60 m	2.60, 2H, m	6.28, 1H, d (16.0)	2.35 m; 2.50 m
17	1.59, 2H, m	4.10, m	6.73, 1H, dt (16.0, 7.6)	1.56, 2H, m
18	1.36, 2H, m	1.32, m; 1.60, m	2.30, 2H, m	1.32, 2H, m
19	2.20 m	2.44 m	2.36, 1H, m	2.00 m
20	2.20 m	2.34 m	2.30, 1H, m	2.26 m
	2.70 dd (17.0, 4.0)	2.76 m	2.68, 1H, m	2.70 dd (16.8, 4.0)
22	0.90, 3H, d (7.5)	0.92, 3H, d (7.0)	0.89, 3H, d (7.2)	0.96, 3H, d (7.2)
23	1.91, 3H, s	1.67, 3H, br.s	1.83, 3H, d (1.2)	1.76, 3H, s
24	1.12, 3H, d (6.5)	1.13, 3H, d (7.0)	1.15, 3H, d (6.0)	1.13, 3H, d (6.8)
25	2.20 m	2.32 m	2.30, 1H, m	2.26 m
	2.70 dd (17.0, 4.0)	2.80 m	2.68, 1H, m	2.70 dd (16.8, 4.0)
8-OCH ₃	3.30 s		3.31 s	
NH	8.10 br.s	8.63 br.s	8.0 br.s	8.01 br.s

^a Signals were assigned with the aid of ¹H-¹H gCOSY, HMQC and gHMBC experiments.

Table S2. Summary of ¹H NMR (400MHz) spectral data for compounds **19**, **20**, **22**, and **25** in CDCl₃

Position	19 ^a	20	22 ^a	25 ^a
2	2.12, m; 2.36, m	*	2.14, m; 2.42, m	2.14, m; 2.32, m
3	1.52, 2H, m	*	1.30, m; 1.72, m	1.58, 2H, m
4	1.72, 2H, m	*	1.72, 2H, m	1.80, 2H, m
5	2.00, 2H, m	*	2.20, 2H, m	2.20, 2H, m
6	5.38 m, overlap	5.69, dt (16.0, 7.0)	5.61 dt (16.0, 7.2)	5.43, m (overlap)
7	5.38 m, overlap	5.29, dd (16.0, 7.0)	5.41 dd (16.0, 7.2)	5.43, m (overlap)
8	2.18 m; 2.36 m	3.30, dd (10.0, 7.0)	3.73 t (7.2)	2.18, 2H, m
9	3.70, 1H, m	3.65, dd (10.0, 2.5)	3.58 d (9.2)	3.75, m
10	1.88 m	*	1.92 m	1.90 m
11	5.05 m (overlap)	5.04 d (3.0)	5.00 d (3.2)	5.06, br.s
13	5.05 m (overlap)	5.11 d (9.5)	5.07 d (10.0)	5.00, d (10.0)
14	3.46 m	3.45 m	3.38 m	3.37 m
16	6.14, 1H, d (15.6)	2.67 dd (17.5, 8.0); 2.50 dd (17.5, 3.0)	2.40 m; 2.64 m	2.44 m; 2.60 m
17	6.67, 1H, dt (15.6, 7.2)	4.06, m	1.60, 2H, m	4.05, m
18	2.30, 2H, m	1.55, m	1.38, 2H, m	1.55 m
		1.38 ddd (14.5, 9.0, 3.0)		1.32 ddd (14.0, 8.8, 3.2)
19	2.36 m	*	1.84 m	2.22 m
20	2.30 m	2.30 m	2.24 m	2.30 m
	2.66 m	2.78 m	2.70 m	2.78 m
22	0.90, 3H, d (7.2)	0.93, 3H, d (7.5)	0.87, 3H, d (7.2)	0.94, 3H, d (7.2)
23	1.73, 3H, s	1.84, 3H, d (1.0)	1.77, 3H, s	1.77, 3H, br.s
24	1.11, 3H, d (6.8)	1.14, 3H, d (7.0)	1.09, 3H, d (6.8)	1.13, 3H, d (6.8)
25	2.30 m	2.30 m	2.24 m	2.36 m
	2.66 m	2.78 m	2.70 m	2.82 m
8-OCH ₃		3.35 s		
NH	8.22 br.s	8.00 br.s	8.76 br.s	8.22 br.s

^a Signals were assigned with the aid of ¹H-¹H gCOSY, HMQC and gHMBC experiments. * Unassigned signals.

Table S3. Summary of ¹H NMR (400 MHz for **26**, 500 MHz for **21**, **23**, **24**, and **27**) spectral data in CDCl₃^a

Position	21	23	24	26 ^a	27
2	*	*	*	2.18, m; 2.42, m	*
3	*	*	*	1.30, m; 1.76, m	*
4	*	*	*	1.80, 2H, m	*
5	*	1.98, m; 2.10, m	1.95, m; 2.12, m	1.84, m; 2.20, m	*
6	5.47, dt (15.5, 7.0)	5.58, m (overlap)	5.50, ddd (16.0, 8.5, 7.5)	5.61, dt (16.0, 7.2)	5.58, m (overlap)
7	5.36, dd (15.5, 7.0)	5.50, m (overlap)	5.30, dd (16.0, 4.5)	5.40, dd (16.0, 6.8)	5.58, m (overlap)
8	*	3.95, m	3.38, m	3.71, dd (9.6, 6.4)	*
9	*	1.90, 2H, m	1.92, 2H, m	3.60, dd (9.2, 2.0)	*
10	*	2.10, m	2.10, m	1.94 m	*
11	4.94 d (2.5)	4.96, d (3.0)	4.98, d (4.0)	5.02, d (3.2)	5.05, br.s
13	5.02 d (10.0)	5.10, d (10.0)	5.18, d (9.5)	5.10, d (9.6)	5.00, d (10.0)
14	3.36 m	3.38, m	3.38, m	3.50 m	3.38, m
16	2.54 dd (17.5, 8.0); 2.45 dd (17.5, 3.0)	2.50, 2H, m	2.50, 2H, m	6.22, d (15.6)	*
17	4.04, m	4.05, m	4.05, m	6.71, dt (15.6, 7.2)	4.00, m
18	1.58, m	1.30, m	1.30, m	2.30, 2H, m	1.28, m
	1.34 ddd (14.5, 7.0, 3.0)	1.50, m	1.60, m		1.56, m
19	2.48, m	2.50, m	2.50, m	2.36 m	*
20	2.33 m	2.30, m	2.40, m	2.30 m	2.30, m
	2.77 m	2.78, m	2.78, m	2.72 m	2.78, m
22	0.84 (7.0)	0.90 (7.0)	0.90 (7.0)	0.85 (7.6)	0.90 (7.0)
23	1.76 (1.0)	1.78, br.s	1.78, br.s	1.79, d (1.2)	1.78, br.s
24	1.13 (6.5)	1.08 (7.0)	1.08 (7.0)	1.12 (6.4)	1.08 (7.0)
25	2.33 m	2.30, m	2.40, m	2.30 m	2.30, m
	2.77 m	2.78, m	2.78, m	2.72 m	2.78, m
NH	8.02 br.s	7.90, br.s	7.98, br.s	8.82 br.s	8.05, br.s

^a Signals were assigned with the aid of ¹H-¹H gCOSY, HMQC and gHMBC experiments. *Unassigned signals.

Table S4. ^{13}C NMR spectral data of compounds **6**, **8**, **17-19**, and **22** in CDCl_3 ^a

Position	6 ^b	8 ^b	17 ^c	18 ^c	19 ^c	22 ^c
1	172.4	173.1	172.5	173.1	173.1	173.2
2	34.7	33.2	34.6	34.8	34.8	34.6
3	26.7	24.0	26.6	28.2	28.1	26.5
4	22.9	23.0	22.8	23.1	23.1	22.7
5	30.5	30.4	30.4	30.5	30.9	29.9
6	135.8	131.7	135.7	133.8	133.8	133.9
7	129.8	126.5	129.7	126.8	126.9	131.9
8	82.8	130.6	82.7	38.2	38.3	73.3
9	72.4	130.7	72.4	74.3	73.9	73.1
10	38.4	33.7	38.4	41.4	41.5	38.3
11	79.5	82.4	79.6	77.2	77.2	79.2
12	135.8	134.9	134.6	135.7	135.8	134.4
13	127.3	129.1	127.1	124.7	124.9	127.3
14	46.2	46.6	44.8	46.1	44.6	46.1
15	211.0	212.1	199.8	211.2	200.0	211.0
16	40.2	47.6	131.5	40.1	131.2	40.0
17	20.6	64.7	141.3	20.6	141.6	20.2
18	34.4	41.0	37.4	34.3	37.3	34.1
19	30.5	27.2	29.8	31.0	29.7	30.4
20	38.0	38.5	37.6	37.9	37.5	38.0
21	172.4	172.7	171.7	172.4	172.0	172.4
22	11.3	17.7	11.2	11.0	11.0	11.1
23	13.9	14.9	13.7	14.8	14.5	13.9
24	16.1	17.1	15.6	16.3	16.0	16.1
25	38.0	37.2	37.6	37.9	37.5	37.8
26	172.4	172.6	171.7	172.4	172.0	172.4
8-OCH ₃	56.7		56.7			

^a Signals were assigned with the aid of ^1H - ^1H gCOSY, HMQC and gHMBC experiments. ^b Measured at 125 MHz, ^c Measured at 100 MHz

Table S5. Summary of ^{13}C NMR (125MHz) spectral data for compounds **21**, and **23-27** in CDCl_3

Position	21 ^a	23 ^a	24 ^a	25 ^b	26 ^b	27 ^a
1	173.8	172.9	172.9	173.5	172.4	173.8
2	34.8	34.5	34.4	34.8	34.6	34.6
3	28.0	25.9	26.2	28.1	26.4	28.6
4	23.4	23.0	23.4	23.1	22.7	23.4
5	31.0	30.7	30.6	30.9	30.4	30.4
6	124.0	135.3	135.4	136.5	133.9	135.3
7	128.5	133.2	134.8	126.8	131.9	136.8
8	34.0	81.4	72.1	38.2	73.4	70.7
9	28.7	39.3	41.0	74.2	73.0	41.1
10	34.8	33.6	33.4	41.3	38.3	30.3
11	78.6	79.1	79.0	76.7	79.5	79.1
12	136.5	133.2	131.9	133.9	134.7	132.7
13	128.5	126.4	126.2	124.1	127.2	123.7
14	46.8	46.7	46.7	46.7	44.8	46.6
15	212.6	212.5	212.5	212.3	199.8	212.6
16	41.4	47.5	47.6	47.4	131.1	47.3
17	65.3	65.1	65.2	65.2	141.9	65.2
18	41.2	41.1	41.3	41.1	37.5	42.0
19	27.4	27.4	27.3	27.3	29.6	27.3
20	38.7	38.7	38.6	38.6	37.5	38.6
21	172.5	172.4	172.3	172.6	172.6	172.5
22	16.0	17.5	17.4	11.0	11.1	15.4
23	15.2	15.2	15.1	14.7	13.8	15.2
24	15.7	16.1	16.2	15.8	15.8	15.9
25	37.4	37.4	37.4	37.4	37.3	37.4
26	172.5	172.3	172.2	172.5	172.4	172.3
8-OCH ₃		56.2				

^a Measured at 125 MHz. ^b Measured at 100 MHz