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Sandwich and Half-Sandwich Derivatives of Platensimycin: Synthesis and Biological Evaluation

Malay Patra,[†] Gilles Gasser,[†,‡] Michaela Wenzel,[§] Klaus Merz,[†] Julia E. Bandow,[§] and Nils Metzler-Nolte*[,†]

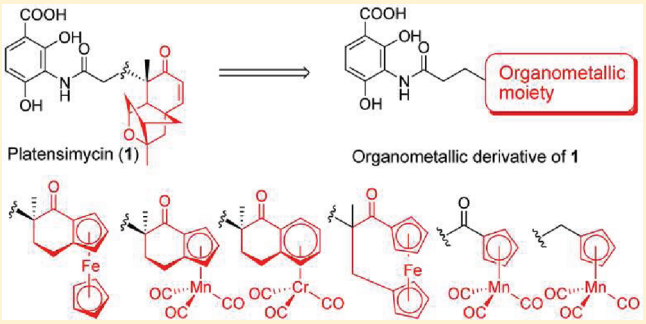
[†]Lehrstuhl für Anorganische Chemie I-Bioanorganische Chemie, Fakultät für Chemie und Biochemie, Ruhr-Universität Bochum, Gebäude NC 3 Nord, Universitätsstrasse 150, D-44801 Bochum, Germany,

[‡]Institute of Inorganic Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland;

[§]Lehrstuhl für Biologie der Mikroorganismen, Fakultät für Biologie und Biotechnologie, Ruhr-Universität Bochum, Universitätsstrasse 150, D-44801 Bochum, Germany.

Supporting Information

ABSTRACT: The multistep synthesis and biological evaluation of five structurally diverse, chiral and achiral $CpMn(CO)_3$ (**4**, **7** and **8**), (η^6-arene)$Cr(CO)_3$ (**5**), and [3]ferrocenophane-1-one (**6**) containing platensimycin (**1**) derivatives are described in this report. The structures were inspired by the antibiotic platensimycin. All the chiral compounds presented in this report are racemates. The new compounds were unambiguously characterized by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, IR spectroscopy, and elemental analysis and in certain cases by X-ray crystallography (**4**, **16**, **18**, and **29**). The antibacterial and antitumor activity of selected derivatives was tested. Molecular modeling suggests that the derivatives described here may well fit into the active site of the FabF enzyme, which is the biological target of platensimycin. Hence, the antimicrobial activities of our new bioorganometallices **4**−**8** and the protected amide intermediates **15**, **17**, **18**, **23**, **28**, **29**, and **31** were tested against various Gram-positive and Gram-negative bacterial strains. However, all compounds were inactive up to concentrations of 180 μg/mL. The cytotoxicity of compounds **4** and **6** and the protected amide intermediates **15**, **17**, **18**, **23**, **28**, **29**, and **31** was tested against HepG2 and PT45 mammalian cancer cell lines. Surprisingly, all compounds containing a trimethylsilylethyl ester functionality at the aromatic ring (**17**, **23**, **29**, and **31**) displayed rather high cytotoxicity between 2 and 9 μM.



INTRODUCTION

The derivatization of bioactive organic molecules with organometallics was shown to be an attractive strategy to modify the inherent properties of biomolecules.[1−4] The most prominent examples are undoubtedly the derivatization of known anticancer and antimalarial drugs with ferrocene.[3,5,6] Ferroquine, a ferrocenyl derivative of the known antimalarial drug chloroquine, was found to overcome the resistance problem of chloroquine.[7−9] Importantly, ferroquine has recently successfully passed clinical phase II trials and is now undergoing field testing. Ferrocifens are another successful example of such derivatization. These ferrocene-modified tamoxifens, developed by Jaouen et al., exhibit activity against hormone-independent breast cancer, where hydroxytamoxifen and tamoxifens are inactive.[10] Apart from that, organometallic compounds have also found application as enzyme inhibitors.[11] With more and more organometallic compounds receiving attention for applications in medicinal organometallic chemistry, the need arises for the development of multistep synthetic routes to complicated structures containing organometallic moieties.

Despite the success of the "ferrocene derivatization" in medicinal organometallic chemistry,[1,12] other fairly stable metallocene derivatives such as [3]ferrocenophane, $CpMn(CO)_3$ (cymantrene), and (η^6-arene)$Cr(CO)_3$ have received, surprisingly, much less attention. [3]Ferrocenophane was recently introduced as an attractive pharmacophore in the development of cytotoxic agents for hormone-refractory breast cancer cells.[13,14] Apart from the carbonyl metal immunoassay (CMIA),[15,16] Schatzschneider et al. have demonstrated that the conjugation of cymantrene to the cell-penetrating peptide (CPP) hCT(18-32)-k7 modulates the intracellular distribution of the CPP and induces cytotoxicity against MCF-7 cells.[17] Schmalz et al. reported several (η^6-arene)$Cr(CO)_3$ derivatives of the anti-inflammatory diterpenes as specific inhibitors of the NOD2 signaling pathway.[18] Very recently, Nordlander et al. disclosed a (η^6-benzene)$Cr(CO)_3$ derivative of the antimalarial

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drug chloroquine, which is 2 times more active compared to its purely organic analogue.[19]

Since the discovery of the naturally occurring antibiotics platensimycin (**1**; Figure 1)[20] and platencin (**2a**; Figure 1),[21]

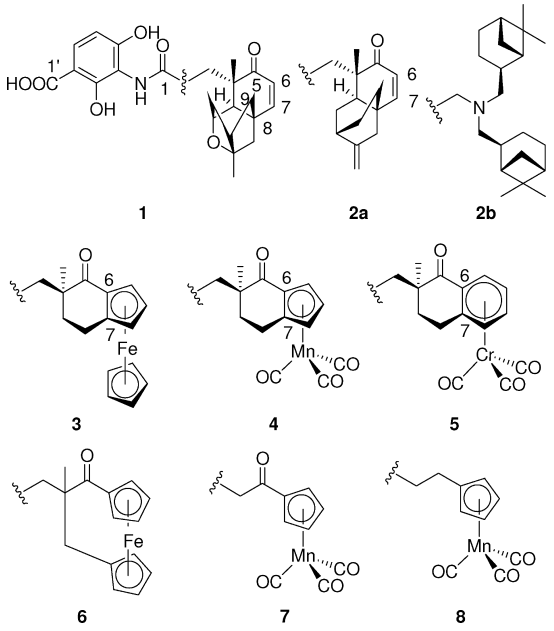

Figure 1. Structures of platensimycin (**1**), platencin (**2a**), a dialkylamino derivative (**2b**), and organometallic derivatives (**3**–**8**) of **1**.

numerous synthetic routes have been developed not only to **1** and **2a** but also to various derivatives for structure–activity relationship (SAR) studies.[22−24] Strikingly, a recent publication by Sintim et al. showed that the complex tetracyclic cage of **1** can be replaced by simple dialkyl amine moieties (**2b**; Figure 1) without losing the biological activity.[25] Concurring with the emergence of organic derivatives of **1** and **2a**, we embarked on a project to investigate the possibility of replacing its complex tetracyclic cage by bulky and lipophilic organometallic cores. The synthesis and biological evaluation of $(\eta^6$-arene$)Cr(CO)_3$ and ferrocene based derivatives of **1** was reported.[26−29] Recently, we published the synthesis of a C6–C7 ferrocene fused derivative (**3**; Figure 1) of **1**.[30] As a continuation of these initial studies, we report herein the synthesis of five new derivatives of **1** (**4**–**8**; Figure 1) as well as the antimicrobial and cytotoxic activities of these compounds and the protected amide derivatives **15**, **17**, **23**, **28**, **29**, and **31** (Schemes 1–3). Both of the bioorganometallics **3** and **6** contain ferrocene but possess significant structural differences. While **3** consists of a homoannular ferrocene moiety, the [3]ferrocenophane-1-one of **6** is a heteroannular C_3 bridged and slightly strained ferrocene moiety. Bioorganometallics **4** and **5** are the homologues of **3**, and the size of the organometallic core increases in the order ferrocene < cymantrene < $(\eta^6$-benzene$)Cr(CO)_3$. Importantly, while compounds **3**–**6** are chiral molecules, **7** and **8** are relatively simple and achiral in nature. These structurally diverse metallocene-containing derivatives of **1** extend the chemical space for further SAR studies on platensimycin analogues.

RESULTS AND DISCUSSION

Manual Docking of 4 and 6 into the FabF Enzyme Pocket. Platensimycin exerts antibacterial activity by inhibiting one of the fatty acid biosynthesis enzymes, namely FabF.[20] With this biological target in mind, we performed manual computer docking experiments to model our organometallic platensimycin derivatives in a way that they could also fit within this pocket and hence have potentially a mode of action similar to that of platensimycin. Of note, we have previously shown, by manual computer docking experiments, that the S,S_P enantiomer of **3** fits nicely in the active site of the FabF enzyme and that the C6–C7 fused ferrocene occupies a pocket similarly to the C8–C9 fused tetracyclic cage of **1**.[30] The results of similar experiments with (S,S_P)-**4** and (S)-**6** are presented in Figure 2. Both fit well in the active site when superimposed

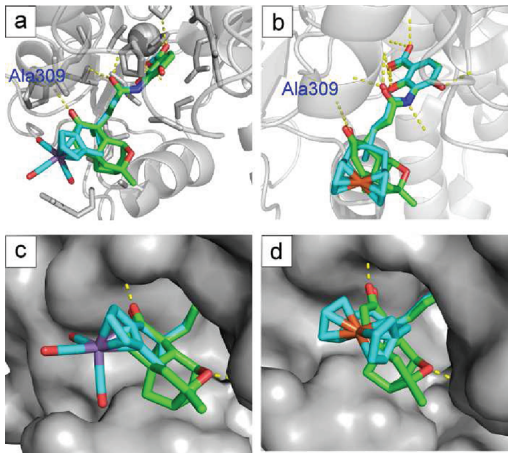

Figure 2. Manual superimposition of (S,S_P)-**4** (cyan) (a and c) and (S)-**6** (cyan) (b and d) on **1** (lime green) bound to the FabF enzyme. Reasonable atomic coordinates for (S,S_P)-**4** and (S)-**6** were obtained from the X-ray single-crystal structures of *rac*-**4** and *rac*-**29** (the protecting group was manually substituted by hydrogen). The obtained models were manually fitted into the reported X-ray crystal structure of **1** bound to FabF enzyme (PDB code 2gfx).[20]

manually on **1** bound to its target enzyme FabF. The keto carbonyl oxygen in both cases is capable of forming H bonds with the active site amino acid residue Ala309 as the keto carbonyl of **1** does. As expected, in the case of (S,S_P)-**4**, cymantrene occupied the same pocket as ferrocene for (S,S_P)-**3**.[30]

Synthesis and Spectroscopic Characterization. It should first be noted that all chiral compounds described in this report are racemates. The synthesis of the cymantrene-containing **4**, **7**, and **8** was initiated from commercially available cymantrene and is presented in Scheme 1. Carboxylic acid **9** was prepared following a literature procedure.[31] Reduction of the keto group of **9** using Zn(Hg) and concentrated HCl (Clemmensen reduction) gave **10** in 73% yield.[32−34] The cymantrene fused cyclohexenone **11** was prepared by polyphosphoric acid mediated intramolecular cyclization of **10**.[34] Afterward a synthetic route similar to that developed previously during our synthesis of C6–C7 ferrocene fused platensimycin derivative **3** was applied to synthesize the C6–C7 cymantrene fused platensimycin derivative **4** from **11**.[30] Treatment of **11** with KHMDS and MeI gave exclusively the exo-methylated ketone **12** in 62% yield. As expected, the ^{1}H NMR spectrum of **12** showed a doublet for the *exo*-CH_3 group at 1.19 ppm together with other protons from the cymantrene moiety. The Michael addition reaction of **12** to methyl acrylate in the presence of potassium *tert*-butoxide (KO^tBu) led to the formation of the methyl ester **13** as a single diastereomer in

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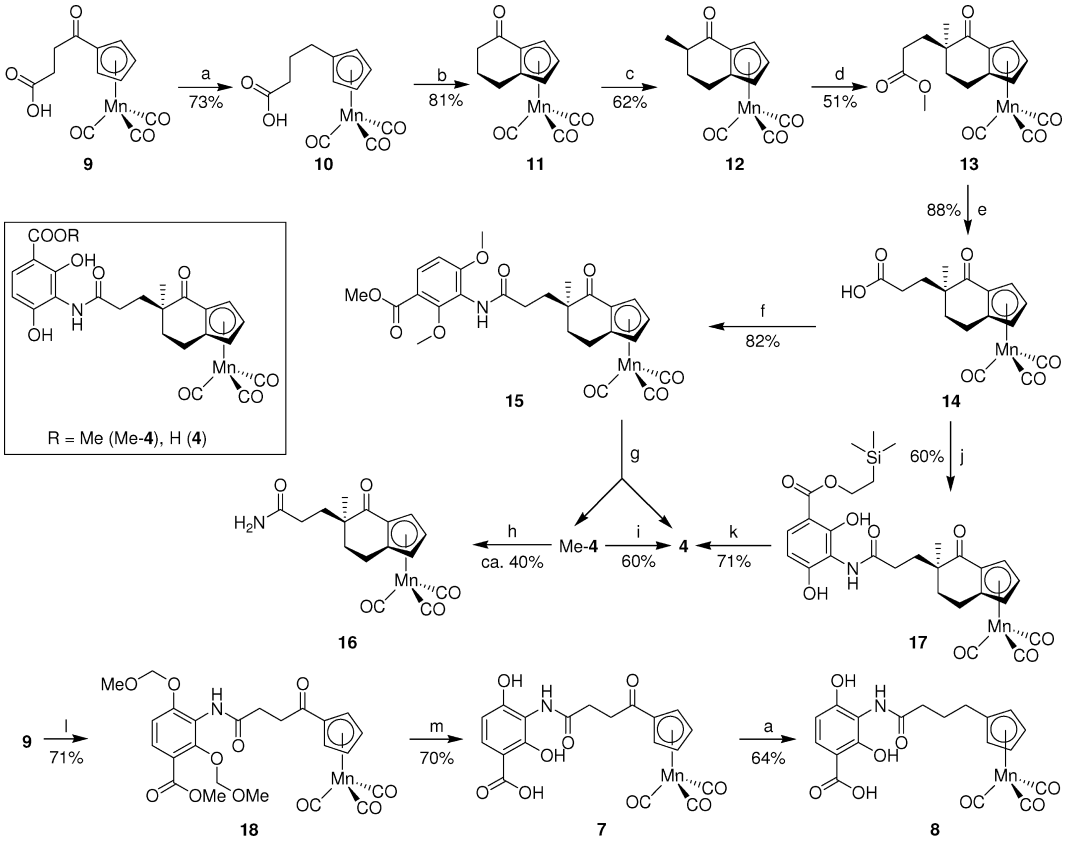
Scheme 1. Synthesis of Cymantrene-Containing 4, 7, and 8[a]



[a]Reagents and conditions: (a) Zn(Hg), concentrated HCl; (b) polyphosphoric acid, 80 °C; (c) KHMDS, HMPA, MeI, THF; (d) KO^{t}Bu, methyl acrylate, ^{t}BuOH, Et_2O; (e) 1 M aqueous NaOH, THF, MeOH; (f) methyl 3-amino-2,4-dimethoxybenzoate, HATU, DIPEA, DMF; (g) BBr_3, $CHCl_3$; (h) LiOH, H_2O, THF; (i) degassed 1 M aqueous NaOH, THF, MeOH, N_2 atmosphere; (j) 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate, HATU, DIPEA, DMF; (k) TASF, DMF; (l) methyl 3-amino-2,4-bis(methoxymethoxy)benzoate, HATU, DIPEA, DMF; (m) LiOH·H_2O, THF, H_2O, and then 4 M HCl in dioxane.

51% yield. After purification by flash column chromatography, the ^{1}H NMR spectrum of **13** showed a clean singlet at 1.17 ppm corresponding to the *endo*-C*H*$_3$ group. As reported earlier for the similar ferrocene-containing cyclohexanone derivative,[30] the Michael addition proceeded with a high degree of diastereoselectivity due to the preferentially less hindered exo face (opposite to the Mn(CO)$_3$ unit) approach of the electrophiles. Treatment of **13** with aqueous NaOH yielded the desired carboxylic acid **14** in 88% yield. The formation of **14** was confirmed by the disappearance of the COOC*H*$_3$ signal in its ^{1}H NMR spectrum. Two peaks centered at *m*/*z* 714.80 and 356.85 corresponding to $[2M - H]^-$ and $[M - H]^-$ species were observed in the ESI-MS (negative detection mode) spectrum. HATU-mediated peptide coupling of **14** with methyl 3-amino-2,4-dimethoxybenzoate[30,35] gave amide **15** in 82% yield. Treatment of **15** with BBr_3 afforded the desired bioorganometallic **4**, together with its methyl ester Me-**4**. Me-**4** could be converted to **4** by treatment with a deoxygenated 1 M aqueous NaOH/MeOH/THF mixture under an inert atmosphere. The ^{1}H NMR spectrum of **4** showed a singlet at 1.12 ppm corresponding to the *endo*-C*H*$_3$ group together with three broad singlets at 5.04, 5.30, and 5.42 ppm corresponding to the cymantrene moiety and two doublets at 6.40 and 7.56 ppm for the benzene ring protons. A clean peak at *m*/*z* 507.79 for the $[M - H]^-$ species was observed in the ESI-MS (negative detection mode) spectrum. Two strong stretching vibration bands at 2019 and 1921 cm^{-1} characteristic for the Mn−*C*O in C_{3v} symmetry were observed in the IR spectrum of **4**. Surprisingly, we discovered that the treatment of Me-**4** with aqueous LiOH·H_2O/THF in the absence of inert conditions gave an undesired byproduct, which was structurally characterized as the amide **16** from its ESI-MS (positive detection mode) and by X-ray crystallography (see Figure 3b). Importantly, the formation of **16** from Me-**4** is very unusual as the process involves the cleavage of a C(sp^2)−N bond. One possible mechanism could be the formation of an *o*-quinone monoimine intermediate from Me-**4** or **4** under oxidative basic reaction conditions which would rapidly hydrolyze to give **16** and an *o*-quinone derivative (see Figure S4 in the Supporting Information for details). Alternatively, amide coupling of **14** with 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate[36] gave the trimethylsilyl protected derivative **17** that could then be deprotected easily by treatment with tris(dimethylamino)-sulfonium difluorotrimethylsilicate (TASF) to give the desired analogue **4** in 71% yield.

Synthesis of the achiral bioorganometallics **7** and **8** was relatively straightforward. Amide coupling of **9** with methyl 3-amino-2,4-bis(methoxymethoxy)benzoate[37] gave the protected amide **18**, which was then deprotected using aqueous LiOH and then 4 N HCl in dioxane to provide **7** in 70% yield. The ^{1}H NMR spectrum of **7** showed two signals at 5.04 and 5.65 ppm corresponding to the cymantrene moiety together with two doublets for the aromatic protons at 6.49 and 7.62 ppm, respectively. **8** was obtained in 64% yield by Clemmensen

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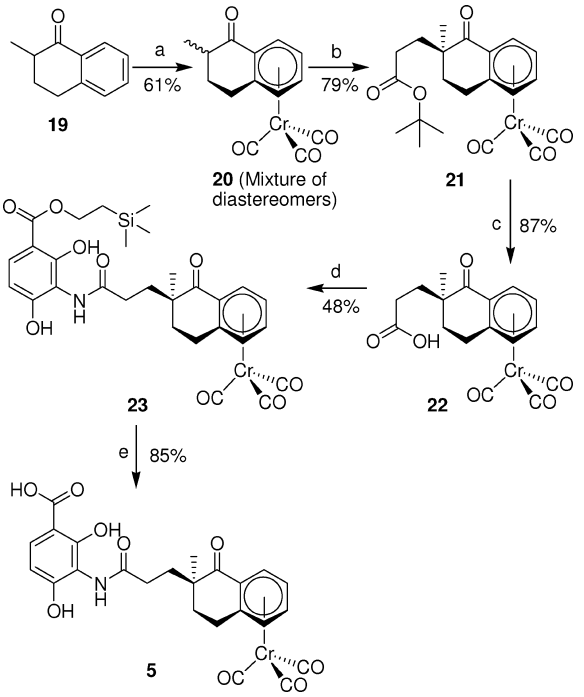
reduction of **7** using Zn(Hg) and concentrated HCl. In the ^{13}C NMR spectrum of **8**, the signal at 199.4 ppm corresponding to the keto group of **7** vanished with the appearance of the new CH_2 signal at 26.3 ppm.

As shown in Scheme 2, the (η^6-arene)$Cr(CO)_3$ containing bioorganometallic **5** was prepared in a five-step synthesis

Scheme 2. Synthesis of 5[a]



[a]Reagents and conditions: (a) $Cr(CO)_6$, Bu_2O, THF, 140 °C; (b) KO^{t}Bu, *tert*-butyl acrylate, ^{t}BuOH, Et_2O; (c) 1 M aqueous NaOH, MeOH, THF; (d) 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate, HATU, DIPEA, DMF; (e) TASF, DMF.

starting from 2-methyl-1-tetralone (**19**). In the first step, the metalation of **19** with $Cr(CO)_6$ in a deoxygenated Bu_2O/THF 9/1 (v/v) mixture provided compound **20** as a mixture of two diastereomers (the ratio of *exo*- and *endo*-CH_3 diastereomers was ~60:40) in 61% combined yield.[38] The separation of the diastereomers was not necessary for the next step, since epimerization occurs. Meyer et al. reported that the base-catalyzed Michael addition of methyl vinyl ketone with **20** proceeds with a high degree of diastereoselectivity and the *exo*- and *endo*-CH_3 diastereomers were indeed obtained in a ratio of 13:87.[39] We used slightly different reagents and reaction conditions. Treatment of **20** with *tert*-butyl acrylate in the presence of KO^{t}Bu gave only the *endo*-CH_3 epimer **21** in 79% yield. The absence of the undesired *exo*-CH_3 epimer within the detection limit was confirmed from the ^1H NMR spectrum. **21** was then treated with aqueous NaOH to obtain the desired carboxylic acid **22**, which was then coupled with 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate[36] to yield the intermediated amide **23**. Treatment of **23** with TASF in DMF gave the desired bioorganometallic **5** in 85% yield. The ^1H NMR spectrum of **5** showed, as expected, a singlet at 1.16 ppm corresponding to the *endo*-CH_3 group together with the signals for the CH_2 protons and all the benzene ring protons. ESI-MS (negative detection mode) spectrum showed a clean peak at 517.88 corresponding to $[M - H]^-$ species of **5**.

The synthetic route for the preparation of the [3]ferrocenophane-1-one based bioorganometallic **6** is presented in Scheme 3. [3]Ferrocenophan-1-one (**24**) was prepared following a literature procedure.[40] Methylation of **24** with KHMDS and MeI gave **25** in 67% yield. A considerable amount of **24** was found to be unreacted but could be recovered easily during the purification by flash column chromatography. Increased amounts of either KHDMS or MeI did not improve the conversion. The ^1H NMR spectrum of **25** showed a doublet at 1.11 ppm for the CH_3 group together with the other expected signals. Treatment of **25** with *tert*-butyl acrylate in the presence of KO^{t}Bu led to the formation of *tert*-butyl ester **26** in 65% yield, together with a trace amount of the carboxylic acid **27**. Attempts to hydrolyze the ^{t}Bu ester of **26** with aqueous NaOH or LiOH gave carboxylic acid **27** together with a considerable amount of unidentified impurities. However, Et_3SiI-mediated ester hydrolysis of **26** proceeded smoothly and the desired carboxylic acid **27** was obtained in 82% yield. The formation of **27** was confirmed by the disappearance of the $C(CH_3)_3$ signal in its ^1H NMR spectrum. A clean peak at m/z 326.04 corresponding to the $[M]^+$ species was observed in the ESI-MS (positive detection mode) spectrum. Amide coupling of **27** with methyl 3-amino-2,4-dimethoxybenzoate yielded the protected amide **28** in 57% yield. Treatment of **28** with BBr_3 afforded a chromatographically separable mixture of **6** and its methyl ester Me-**6**. Conversion of Me-**6** to **6** was carried out using deoxygenated 1 M aqueous NaOH/MeOH/THF under inert conditions. However, slow decomposition of **6** was observed under these reaction conditions. The formation of a large amount of side products was observed, and this is probably due to the oxidative decomposition of the [3]ferrocenophan-1-one moiety under the basic reaction conditions. Indeed, as described earlier, similar problems during the ester hydrolysis of **26** under basic conditions were noticed. These observations suggest that the [3]ferrocenophan-1-one moiety is somewhat sensitive to hydroxyl bases. In order to avoid basic conditions in the deprotection step, we employed 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate as previously used for the synthesis of **4** and **5**. Thus, amide coupling of **27** with 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate gave compound **29**, which could be then deprotected by treatment with TASF to obtain the desired bioorganometallic **6** in 78% yield. The presence of **6** was confirmed from its ^1H NMR spectrum, with a singlet at 1.32 ppm corresponding to the CH_3 group together with all the signals expected from the [3]ferrocenophan-1-one and the benzoic acid unit, respectively. Additionally, in its ESI-MS (positive detection mode) spectrum, two signals centered at m/z 477.02 and 499.97 corresponding to $[M]^+$ and $[M + Na]^+$ species unambiguously proved the presence of **6**. Compound **31** was synthesized in one step from the carboxylic acid **30** (Scheme 3).[30]

X-ray Crystallography. The molecular structures of **4**, **16**, **18**, and **29** were confirmed by the determination of their respective X-ray single-crystal structures. ORTEP plots are presented in Figures 3 and 4. Table S1 (in the Supporting Information) contains the relevant crystallographic data and parameters.

The cymantrene-containing compounds **4**, **16**, and **18** crystallize in triclinic $P\bar{1}$, monoclinic $P2_1/c$, and orthorhombic *Pbca* space groups, respectively. Neither the metal fragment nor the organic part in the structures possess any unusual structural features.[31] In the solid state of **4**, both phenolic hydroxide groups form intramolecular hydrogen bonds to the carbonyl group of the carboxylic acid and the amide moiety (see Figure 3a).

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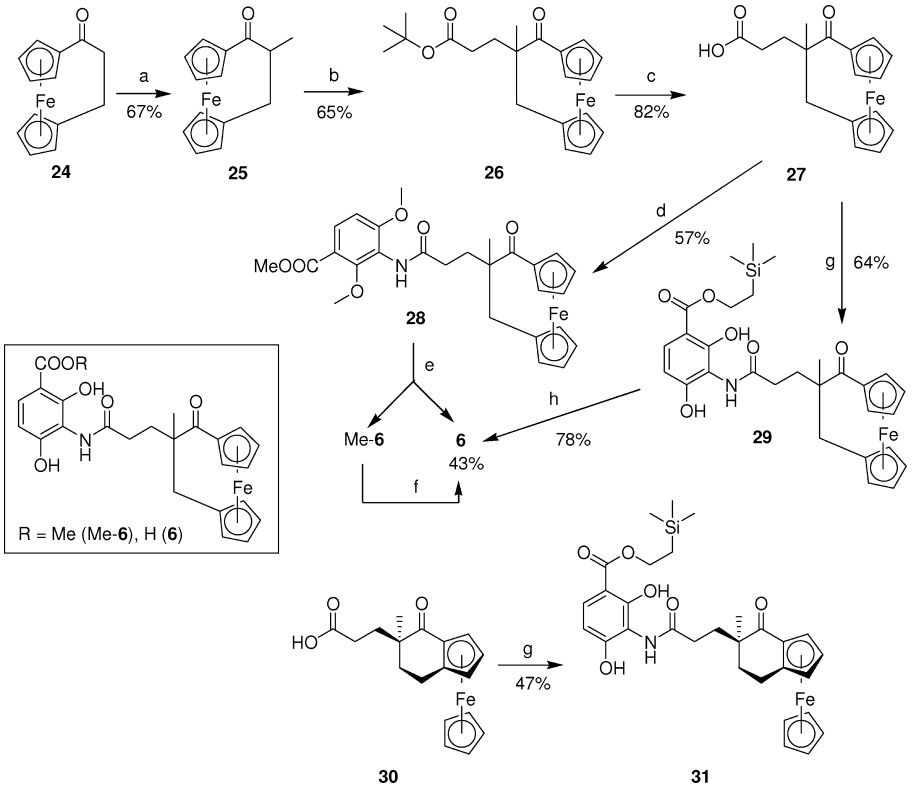
Scheme 3. Synthesis of [3]Ferrocenophan-1-one Based Bioorganometallic 6[a]



[a]Reagents and conditions: (a) KHMDS, HMPA, MeI, THF; (b) KO^{t}Bu, *tert*-butyl acrylate, ^{t}BuOH, Et_2O; (c) Et_3SiI, CH_2Cl_2; (d) methyl 3-amino-2,4-dimethoxybenzoate, HATU, DIPEA, DMF; (e) BBr_3, $CHCl_3$; (f) 1 M aqueous NaOH, THF, MeOH, N_2 atmosphere; (g) 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate, HATU, DIPEA, DMF; (h) TASF, DMF.

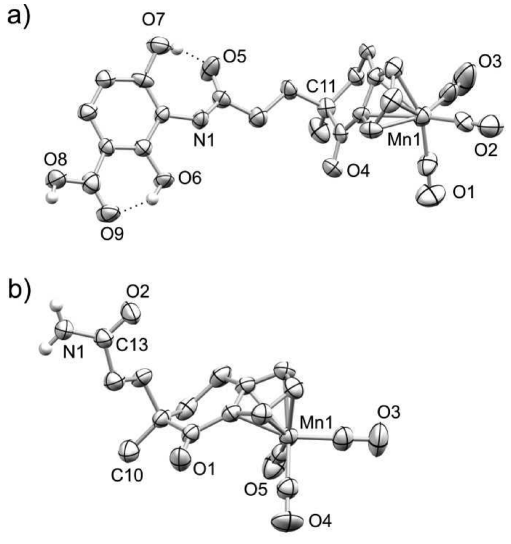


Figure 3. ORTEP plots of **4** (a) and **16** (b). Ellipsoids are drawn at the 50% probability level. Except for the OH in **4** and NH in **16**, all other hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg) of **4**: Mn(1)−centroid Cp(C1−5) = 1.762, average Mn(1)−CO = 1.79(4), C(2)−C(9) = 1.516(9), C(3)−C(12) = 1.447(10); Mn(1)−C(2)−C(9) = 128.7(5), Mn(1)−C(3)−C(12) = 123.6(5), average CO−Mn(1)−CO = 92.5. Selected bond lengths and angles of the metal−organic part in **16** are similar to those presented for **4**.

As mentioned earlier, the single-crystal X-ray structure determination of **16** helped us to identify the unexpected compound **16** as the main side product during the attempted transformation of Me-**4** to **4** by treatment with LiOH in the absence of an inert atmosphere (for hydrogen-bonding interactions in the single crystals of **4**, **16**, and **18**, see Figures S1−S3 in the Supporting Information).

Compound **29** crystallized in the monoclinic $P2_1/c$ space group. As shown in Figure 4b, the OH groups of the [3]ferrocenophan-1-one containing amide **29** form intramolecular hydrogen bonds in a fashion similar to that observed in the solid state of **4**. The Cp rings are slightly tilted because of the comparatively short C_3 bridge between them and are in a near-eclipsed conformation. The bond lengths and angles of the [3]ferrocenophan-1-one moiety fit well with those reported earlier.[41]

Cytotoxicity Study. An ideal antimicrobial agent is supposed to kill bacteria but not host cells. In order to have a first insight into whether or not our compounds possess any toxicity toward mammalian cells, we determined the IC_{50} values of the organometallics prepared in this study. Compounds **4** and **6** as well as the intermediate protected amide derivatives **15**, **17**, **18**, **23**, **28**, **29**, and **31** were therefore screened against HepG2 and PT45 mammalian cancer cell lines. The cytotoxicity of **5** could not be studied due to solubility problems. Both fully deprotected compounds **4** and **6** showed no cytotoxic activity up to 200 μM concentrations. Surprisingly, it was found that the protected amide derivatives **15**, **17**, **18**, **23**, **28**, **29**, and **31** exhibited cytotoxicity against both cell lines (see Table 1 and see Figure S5 in the Supporting Information for representative examples). When we analyzed the results, it appeared that the cytotoxicity is related to the lipophilic group present in the aromatic moiety of the bioorganometallics. The compounds **17**, **23**, **29**, and **31**, which contain the

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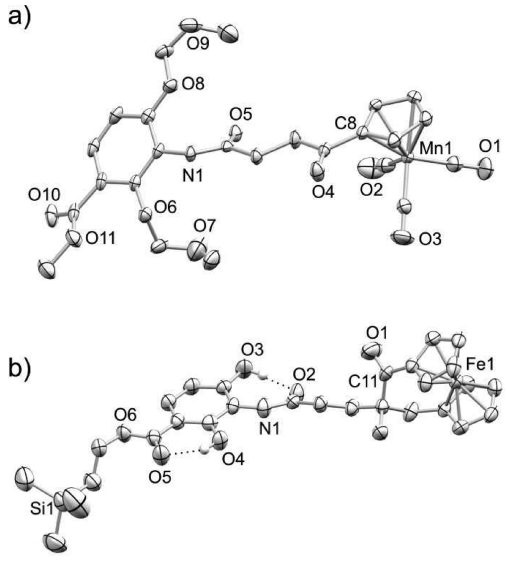

Figure 4. ORTEP plots of **18** (a) and **29** (b). Ellipsoids are drawn at the 50% probability level. Except for the OH in **29**, all other hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg) of **18**: Mn(1)−centroid Cp(C4−8) = 1.766, average Mn(1)−CO = 1.790 (4), C(8)−C(9) = 1.478(5); Mn(1)−C(8)−C(9) = 123.6(2), average CO−Mn(1)−CO = 92.29. Selected bond lengths (Å) and angles (deg) of **29**: Fe(1)−centroid Cp(C1−5) = 1.654, Fe(1)−centroid Cp(C6−10) = 1.654, C(3)−C(11) = 1.506(6), C(11)−C(12) = 1.539(7), C(6)−C(14) = 1.524(7); C(3)−Fe(1)−C(6) = 98.73(19), C(11)−C(3)−Fe(1) = 117.4(3), C(14)−C(6)−Fe(1) = 121.8(3).

Table 1. Cytotoxicity Data of Selected Compounds in This Work against HepG2 and PT45 Mammalian Cancer Cell Lines in the Crystal Violet Assay[a]

	IC_{50} value for two different cell lines (μM)	
compd	HepG2	PT45
15	39.5 ± 5.3	47.0 ± 8.6
17	6.45 ± 0.1	7.3 ± 1.9
18	93.4 ± 3.9	93.2 ± 22.3
23	3.3 ± 0.2	7.3 ± 2.5
28	48.2 ± 5.8	55.5 ± 2.8
29	3.6 ± 0.2	2.3 ± 0.2
31	8.8 ± 3.4	7.8 ± 0.9
cisplatin[42]	2.4 ± 0.4	0.9 ± 0.2

[a]Results represent the averages of two independent experiments with three replicates each.

trimethylsilylethyl ester functionality and two OH groups at the aromatic unit, displayed cytotoxicity in the low micromolar concentration range (2−9 μM). These values are comparable to those of the well-known inorganic anticancer drug cisplatin.[42] However, the cytotoxicity decreased significantly when the OH and the carboxylic acid groups were protected with methyl or methoxymethyl groups (for compounds **15**, **18**, and **28**). While these results give a first hint toward cytotoxic activity, further biological tests will be required to establish the exact mechanism of action of these compounds (e.g., whether the compounds are inducing apoptosis).

Antimicrobial Activity. The antimicrobial activities of our new metallocene-containing platensimycin derivatives **4**−**8** and the protected amide intermediate compounds **15**, **17**, **18**, **23**, **28**, **29**, and **31** were then tested against various Gram-positive (*Staphylococcus aureus* DSM 20231 (type strain), *S. aureus* ATCC43300 (MRSA), *Bacillus subtilis* 168) and Gram-negative (*Escherichia coli* DSM 30083 (type strain) and *Pseudomonas aeruginosa* DSM 50071 (type strain), *Acinetobacter baumannii* DSM 30007 (type strain)) bacterial strains up to 180 μg/mL. Unfortunately, none of these compounds exhibited antibacterial activity against any of the bacterial strains. The lack of activity is perhaps due to insufficient cell permeability of the bioorganometallics, as recently demonstrated for several other synthetic and natural congeners of platensimycin having a modified tetracyclic cage.[24,25]

CONCLUSION

In summary, we have synthesized and characterized structurally diverse sandwich and half-sandwich derivatives of the naturally occurring antibiotic platensimycin (**1**). To the best of our knowledge, the construction of the quaternary center at the C-2 position of the cymantrene fused cyclohexenone **12** with complete diastereoselectivity is described for the first time. Several very interesting synthetic findings were observed in this study, which should help to pave the way for the preparation of further highly functionalized bioorganometallics. The newly synthesized compounds failed to show any antibacterial activity against either Gram-positive or Gram-negative bacterial strains. This could be due to inefficient cell permeability of the bioorganometallics, as observed earlier for some benzene−Cr−tricarbonyl bioorganometallics.[26] However, interestingly, the trimethylsilylethyl esters containing intermediate amides **17**, **23**, **29**, and **31** showed rather impressive cytotoxicity against HepG2 and PT45 mammalian cancer cell lines, approaching IC_{50} values of the well-known anticancer drug cisplatin. Importantly, cerulenin, a fatty acid biosynthesis inhibitor, is currently in preclinical anticancer studies as a part of a combination therapy with rosiglitazone.[43] IC_{50} values of 5 ± 1 and 45 ± 2 μM were determined against prostate cancer cell lines LNCaP, PC-3, and DU-145 for rosiglitazone in the presence and absence of cerulenin, respectively. We are currently performing further studies to understand our unexpected findings and elaborate on the preliminary structure−activity relationship derived herein.

EXPERIMENTAL SECTION

Materials. All chemicals were of reagent grade quality or better, obtained from commercial suppliers and used without further purification. Solvents were used as received or dried over molecular sieves. All preparations were carried out using standard Schlenk techniques. **9**,[31] **24**,[40] methyl 3-amino-2,4-dimethoxybenzoate,[30,35] 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate,[36] methyl 3-amino-2,4-bis(methoxymethoxy)benzoate,[37] was prepared following the literature procedures.

Instrumentation and Methods. *^{1}H and ^{13}C NMR spectra* were recorded in deuterated solvents on Bruker DRX 200, 250, 400, or 600 spectrometers at 30 °C. The chemical shifts, δ, are reported in ppm (parts per million). The residual solvent peaks have been used as an internal reference. The abbreviations for the peak multiplicities are as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). *Infrared spectra* were recorded on an ATR unit using a Bruker Tensor 27 FTIR spectrophotometer at 4 cm^{-1} resolution. Signal intensity is abbreviated br (broad), s (strong), m (medium), and w (weak). *ESI mass spectra* were recorded on a Bruker Esquire 6000. *Crystallographic data* were collected using Bruker-axs SMART 1000 CCD and Rigaku Mercury 375 R/M CCD (XtaLAB mini) diffractometers. The structure was solved by direct methods (SHELXS-97[44]) and refined against F^2 with all measured reflections (SHELXL-97,[44] Palton-Squeeze[45]). Crystallo-

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graphic data were deposited as CIF files in the Supporting Information and also at the CSD (**4**, 823234; **16**, 823236; **18**, 823235; **29**, 823233) *Elemental microanalyses* were performed using a Fisons Carlo Erba EA1108 instrument (CHNS version). The manual docking of experiments of the bioorganometallics with FabF enzyme were done using PyMOL (PyMOL-1_2edu-bin-win32).

Minimum Inhibitory Concentration (MIC) Determination. The antimicrobial activity tests were performed in a microtiter plate assay containing 0.2 mL of Luria Broth medium and appropriate compound concentrations up to 180 μg/mL. Culture media containing appropriate concentrations of compound were inoculated with 10^5 cells/mL and incubated at 37 °C for 18 h. The compounds did not visibly inhibit growth.

Cell Culture and Cytotoxicity Test. Required cells were cultured in RPMI 1640 medium supplemented with 10% fetal calf serum (FCS), 2 mM L-glutamine, penicillin (100 U/mL), and streptomycin (100 μg/mL) in a 5% CO_2 atmosphere. Absolute cell numbers were determined by the crystal violet assay. Cells were seeded in 96-well cell-culture treated microtiter plates (MTP). After seeding, the cells were grown for 24 h under standard conditions. The compounds were dissolved in culture medium with 0.5% DMSO and applied to the cells in 1, 5, 20, 50, 100, 500 μM concentrations for 72 h. Every concentration was tested 6-fold. The cells were fixed with 4% paraformaldehyde (PFA) in phosphate-buffered saline (PBS) for 15 min at room temperature. PFA was eluted two times with PBS, and membranes were permeabilized by Triton X-100 (0.1%) in PBS for 10 min. Afterward, aqueous crystal violet solution (0.04%) was added to the cells and the MTP was mechanically shaken for 1 h. The cells were washed with H_2O (×7), and crystal violet was eluted with 70% EtOH for 3.5 h. The absorbance was determined at 570 nm; the cell biomass could be calculated after subtraction of 24 h presubstance incubation absorbance values. Whenever possible, the inhibitory concentration at 50% growth (IC_{50}) for the assay was determined. The obtained cell mass (%) data were plotted against the concentration on a half-logarithmical scale, and a sigmoidal function fit was performed with Origin 7 (Originlab, Northampton, MA) until the fit converged. IC50 values were directly calculated from the fit function.

Synthesis. *General Procedure for the Amide Coupling (GP1).* To a stirred solution of the carboxylic acid in DMF were added HATU and DIPEA (or NEt_3), and the mixture was stirred for 30 min under an argon atmosphere. The protected amine was then added, and the mixture was stirred at room temperature. After completion of the reaction, the volume of DMF was reduced under vacuum, saturated brine was added to it, and the compound was extracted using ethyl acetate (EtOAc). The organic layer was washed with distilled water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column chromatography was carried out with the residue to obtain the desired amide in pure form.

*4-Cymantrenylbutyric Acid (**10**).*[33] A mixture of granulated Zn (20 g, 0.316 mol) and $HgCl_2$ (3 g, 0.011 mol) in water (20 mL) were stirred for 30 min. Concentrated HCl (10 mL) was slowly added to the mixture, which was further stirred for 10 min. The amalgam was decanted and washed with a 1/1 (v/v) mixture of HCl and water (2 × 15 mL). To this freshly prepared amalgam were added **9** (4 g, 0.013 mol), benzene (20 mL), H_2O (10 mL), acetic acid (5 mL), and concentrated HCl (10 mL), and the mixture was stirred at 100 °C. HCl (2 mL) was added in every 2 h. After 10 h, when the TCL (silica gel, EtOAc/Et_2O 1/1) showed that the reaction was complete, the reaction mixture was cooled to room temperature, diluted with Et_2O (250 mL), and washed repeatedly with water (3 × 50 mL). The product was then extracted with aqueous 1 M NaOH (50 mL) solution, washed with Et_2O (2 × 50 mL), acidified with 1 M HCl (55 mL), and extracted with Et_2O (2 × 200 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. **10** was isolated as a light yellow solid (2.8 g, 73%) and used for the next step without further purification. R_f = 0.49 (silica gel, EtOAc/Et_2O 1/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 2.79−2.97 (m, 2H, CH_2), 2.24−2.61 (m, 4H, 2 × CH_2), 4.61−4.70 (m, 4H, C_5H_4). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) 25.8, 25.9, 27.4, 81.9, 82.1, 105.7, 225.1 (Mn−CO). IR bands (ν): 3113 w, 2948 w, 2576 w, 2004 s, and 1906 s (br, Mn−*CO*), 1712 s, 1686 s, 1480 w, 1424 w, 1408 m, 1316 w, 1222 m, 1186 w, 1022 m, 937 w, 893 w, 838 m, 684 m, 632 s cm^{-1}. ESI-MS (negative detection mode): m/z (%) 288.76 (100) $[M - H]^-$, 578.69 (20) $[2M - H]^-$.

*Cyclic Ketone **11**.*[34] A mixture of **10** (300 mg, 1.03 mmol) and polyphosphoric acid (8 g) was heated at 80 °C for 7 h. Water was added to the reaction mixture, and this mixture was extracted with Et_2O (2 × 50 mL). The organic phase was washed with 1 M HCl (1 × 30 mL), water (5 × 50 mL), and brine (1 × 30 mL), dried over Na_2SO_4, and filtered. Removal of the solvent gave the desired cyclic ketone **11** (230 mg, 81%) as a brown sticky solid. The crude product was used for the next step without further purification. R_f = 0.21 (silica gel, hexane/EtOAc 2.5/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.98−2.16 (m, 2H, CH_2), 2.21−2.39 (m, 1H, CH_2), 2.45−2.70 (m, 3H, CH_2), 4.58−4.70 (m, 1H, C_5H_3), 4.94−5.01 (m, 1H, C_5H_3), 5.10−5.21 (m, 1H, C_5H_3). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) 22.5, 23.1, 38.2, 78.1, 78.4, 86.3, 89.5, 113.4, 197.8, 223.1 (Mn−CO). IR bands (ν): 3107 w, 2951 w, 2016 s, and 1909 s (br, Mn−*CO*), 1683 s, 1436 w, 1411 m, 1316 w, 1281 m, 1245 m, 1170 w, 1140 w, 1043 w, 1029 w, 715 m, 665 s, 651 m, 623 s cm^{-1}. ESI-MS (negative detection mode): m/z (%) 270.96 (100) $[M - H]^-$, 227.02 (50) $[M - CO_2 - H]^-$.

*Compound **12**.* To a solution of the ketone **11** (300 mg, 1.10 mmol) in THF (15 mL) was slowly added 0.5 M KHMDS in toluene (3.3 mL, 1.65 mmol) at −78 °C. The mixture was stirred for 30 min. HMPA (2.3 mL) followed by MeI (1.3 g, 8.82 mmol) was added to the reaction mixture. After 1.5 h at −78 °C, the reaction was quenched with aqueous saturated $NaHCO_3$ solution and extracted with EtOAc (3 × 30 mL). The organic phase was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, hexane/EtOAc 3/1) gave the desired product **12** (195 mg, 62%) as a yellow oil. R_f = 0.56 (silica gel, hexane/EtOAc 3/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.19 (d, 3H, CH_3), 1.81−1.91 (m, 1H, CH_2), 2.11−2.19 (m, 1H, CH_2), 2.58−2.78 (m, 3H, CH_2 and CH), 4.66−4.71 (m, 1H, C_5H_3), 4.92−4.98 (m, 1H, C_5H_3), 5.22−5.29 (m, 1H, C_5H_3). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) 15.1, 20.1, 30.6, 41.2, 78.6, 79.2, 85.3, 88.1, 113.1, 200.3, 223.4 (Mn−CO); IR bands (ν): 2935 w, 2016 s, 1912 s (br, Mn−*CO*), 1684 s, 1454 w, 1434 m, 1376 m, 1274 w, 1169 m, 1145 w, 1033 w, 926 w, 858 m, 665 s, 625 s cm^{-1}. ESI-MS (positive detection mode): m/z (%) 286.85 (90) $[M + H]^+$, 304.10 (100) $[M + H_2O]^+$.

*Methyl Ester **13**.* To a stirred solution of **12** (150 mg, 0.52 mmol) in a mixture of ^{t}BuOH/Et_2O (5 mL, 1/1 (v/v)) was added ^{t}BuOK (117 mg, 1.05 mmol) at 0 °C. After 10 min, methyl acrylate (447 mg, 5.2 mmol) was added to the reaction mixture, and this mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated NH_4Cl, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, hexane/EtOAc 3/1 → 2/1) gave **13** as a light yellow solid (yield 102 mg, 51%). R_f = 0.17 (silica gel, hexane/EtOAc 3/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.17 (s, 3H, CH_3), 1.62−1.80 (m, 1H, CH_2), 1.84−2.08 (m, 3H, CH_2), 2.19−2.54 (m, 3H, CH_2), 2.68−2.84 (m, 1H, CH_2), 3.65 (s, 3H, OCH_3), 4.58−4.62 (s, br, 1H, C_5H_3), 5.01−5.04 (m, 1H, C_5H_3), 5.12−5.16 (s, br, 1H, C_5H_3). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) 19.3, 21.2, 28.6, 29.9, 35.7, 45.1, 51.7, 77.7, 78.4, 87.1, 88.8, 111.7, 173.3, 201.1, 223.5 (Mn−CO). IR bands (ν): 2948 w, 2016 s and 1910 s (Mn−*CO*), 1731 m, 1681 m, 1474 w, 1452 w, 1434 m, 1355 w, 1339 w, 1304 w, 1206 m, 1182 w, 980 w, 850 w, 665 m, 630 s cm^{-1}. ESI-MS (positive detection mode): m/z (%) 394.86 (50) $[M + Na]^+$, 310.22 (100) $[M - 3CO - H + Na]^+$, 282.18 (40) $[M - 4CO - H + Na]^+$. Anal. Calcd for $C_{17}H_{17}MnO_6$: C, 54.85; H, 4.60. Found: C, 54.92; H, 4.73.

*Carboxylic Acid **14**.* To a stirred solution of **13** (160 mg, 0.43 mmol) in MeOH (10 mL) was added 1 M aqueous NaOH (5.1 mL), and the mixture was stirred for 1.5 h at room temperature. MeOH was evaporated, water (30 mL) was added, and the aqueous layer was washed with Et_2O (2 × 20 mL). The aqueous layer was then acidified with 1 M HCl up to pH ∼2 and extracted with Et_2O (2 × 30 mL). The combined organic phase was washed with H_2O and brine, dried over

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anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. The carboxylic acid **14** was obtained as a light yellow sticky solid (yield 136 mg, 88%), which was used for the next step without further purification. For analytical purposes, a small filter column with silica gel was used with pure EtOAc as eluent.

Data for **14** are as follows. R_f = 0.60 (silica gel, EtOAc/MeOH 10/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.19 (s, 3H, CH_3), 1.62−1.83 (m, 1H, CH_2), 1.87−2.84 (m, 3H, CH_2), 2.24−2.57 (m, 3H, CH_2), 2.71−2.86 (m, 1H, CH_2), 4.58−4.62 (s, br, 1H, C_5H_3), 5.01−5.04 (m, 1H, C_5H_3), 5.12−5.16 (s, br, 1H, C_5H_3), 10.7 (1H, br, COO*H*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) 19.2, 21.3, 28.6, 29.7, 35.7, 45.1, 77.8, 78.5, 87.1, 88.6, 111.7, 179.3, 201.1, 223.1 (Mn−CO). IR bands (ν): 2020 s and 1919 s (br, Mn−*CO*), 1699 m, 1685 m, 1484 w, 1434 w, 1380 w, 1303 w, 1186 w, 1157 w, 942 w, 846 w, 664 m, 630 s cm^{-1}. ESI-MS (negative detection mode): *m*/*z* (%) 714.80 (100) $[2M - H]^-$, 356.85 (50) $[M - H]^-$. Anal. Calcd for $C_{16}H_{15}MnO_6$: C, 53.65; H, 4.22. Found: C, 53.95; H, 4.16.

Amide ***15***. The general procedure GP1 was followed: carboxylic acid **14** (358 mg, 1 mmol), methyl 3-amino-2,4-dimethoxybenzoate (422 mg, 2 mmol), HATU (760 mg, 2 mmol), DIPEA (238 mg, 2 mmol), DMF (10 mL), 60 h reaction time, purification by flash column chromatography (silica gel, hexanes/EtOAc 1/1→0/1). **15** was obtained as a light yellow sticky solid (450 mg, 82%). R_f = 0.63 (silica gel, EtOAc). ^{1}H NMR (250 MHz, $CDCl_3$ and trace of CD_3OD): δ (ppm) 1.08 (s, 3H, CH_3), 1.60−1.93 (m, 4H, CH_2), 2.03−2.40 (m, 3H, CH_2), 2.56−2.86 (m, 1H, CH_2), 3.58 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.51 (s, br, 1H, C_5H_3), 4.89−4.94 (m, 1H, C_5H_3), 4.98 (s, br, 1H, C_5H_3), 6.60 (d, 1H, *benzene ring proton*), 7.66 (d, 1H, *benzene ring proton*). ^{13}C NMR (250 MHz, $CDCl_3$ and trace of CD_3OD): δ (ppm) 23.1, 25.0, 34.4, 39.4, 49.2, 55.8, 59.9, 65.5, 81.4, 81.9, 82.4, 91.3, 92.4, 110.7, 116.3, 120.4, 124.1, 135.5, 161.5, 163.5, 170.1, 206.6, 227.2 (Mn−CO). IR bands (ν): 3252 w, 2943 w, 2019 s (Mn−*CO*) 1921s (Mn−*CO*), 1699−1677 s (br), 1595 m, 1434 m, 1354 w, 1272 s, 1187 m, 1146 s, 1041 w, 942 w, 789 w, 751 m, 665 m, 629 s cm^{-1}. ESI-MS (positive detection mode): *m*/*z* (%) 573.89 (100) $[M + Na]^+$, 551.94 (30) $[M + H]^+$.

Amide ***17***. The general procedure GP1 was followed: carboxylic acid **14** (100 mg, 0.27 mmol), methyl 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate (188 mg, 0.70 mmol), HATU (260 mg, 0.81 mmol), DIPEA (104 mg, 0.81 mmol), DMF (4 mL), reaction time 20 h. Flash column chromatography (silica gel, hexane/EtOAc 2.5/1) gave **17** as a light yellow sticky solid (102 mg, 60%). R_f = 0.34 (silica gel, hexane/EtOAc 3/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 0.09 (s, 9H, $Si(CH_3)_3$), 1.14 (m, 2H, $CH_2-CH_2-Si(CH_3)_3$), 1.24 (s, 3H, CH_3), 1.49−2.21 (m, 4H, CH_2), 2.45−2.62 (m, 3H, CH_2), 2.86 (m, 1H, CH_2), 4.43 (m, 2H, $CH_2-CH_2-Si(CH_3)_3$), 4.62 (m, 1H, C_5H_3), 5.04 (m, 1H, C_5H_3), 5.19 (m, 1H, C_5H_3), 6.49 (d, 1H, *benzene ring proton*), 7.56 (d, 1H, *benzene ring proton*), 7.89 (s, 1H, N*H*), 10.85 (s, 1H, O*H*), 11.84 (s, 1H, O*H*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) −1.2, 17.3, 19.2, 21.5, 30.4, 31.2, 36.2, 45.1, 63.9, 77.9, 78.5, 87.3, 88.7, 104.4, 110.9, 111.7, 114.1, 127.5, 153.9, 154.8, 170.4, 173.3, 200.1, 223.3 (Mn−CO). IR bands (ν): 2952 w, 2021 s (Mn−*CO*), 1924s (Mn−*CO*), 1654 m (br), 1595 w, 1534 m, 1452 w, 1387 m, 1250 s, 1145 m, 1040 w, 930 w, 857 s (br), 688 w cm^{-1}. ESI-MS (positive detection mode): *m*/*z* (%) 631.96 (100) $[M + Na]^+$.

Compound ***4*** *from* ***15***. To a stirred solution of the amide **15** (180 mg, 0.33 mmol) in $CHCl_3$ (4 mL) was added BBr_3 (0.31 mL, 3.3 mmol) at −78 °C (just before the solution freezes) under an N_2 atmosphere. The suspension was stirred for 20 h at room temperature. The reaction mixture was then poured into distilled water (20 mL), stirred for a further 30 min, and extracted with EtOAc (3 × 25 mL). The organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column chromatography on silica gel (neat EtOAc → EtOAc/MeOH/AcOH 20/1/0.075) gave Me-**4** (50 mg, light yellow sticky solid), followed by **4** (77 mg, light yellow solid).

To a stirred solution of Me-**4** (50 mg, 0.11 mmol) in a deoxygenated 1/3 (v/v) mixture of THF and MeOH (12 mL) was added 1 M NaOH solution (3.8 mL). The mixture was stirred at 60 °C for 14 h under an N_2 atmosphere. Distilled water (50 mL) was added to the reaction mixture, acidified with 1 M HCl up to pH ∼2, and extracted with EtOAc. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, EtOAc/MeOH/AcOH 20/1/0.075) afforded **4** (24 mg) as a light yellow solid. The combined yield of **4** is 101 mg (60%). Single crystals of **4** were grown by slow evaporation of its solution in a THF/$CHCl_3$ mixture.

Compound ***4*** *from* ***17***. To a stirred solution of amide **17** (100 mg, 0.16 mmol) in DMF (5 mL) was added tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF; 116 mg, 0.41 mmol) at room temperature, and the mixture was heated at 40 °C for 1 h. The reaction mixture was then cooled to room temperature, brine was added to the reaction mixture, and this mixture was extracted with EtOAc (3 × 50 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, EtOAc/MeOH/AcOH 20/1/0.075) gave of compound **4** (yield 59 mg 71%). R_f = 0.35 (silica gel, EtOAc/MeOH/AcOH 20/1/0.075). ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.12 (s, 3H, CH_3), 1.71−1.86 (m, 3H, CH_2), 1.98−2.10 (m, 1H, CH_2), 2.14−2.28 (m, 1H, CH_2), 2.33−2.47 (m, 2H, CH_2), 2.75−2.90 (m, 1H, CH_2), 5.02−5.05 (m, 1H, C_5H_3), 5.28−5.32 (m, 1H, C_5H_3), 5.40−5.43 (m, 1H, C_5H_3), 6.39 (d, 1H, *benzene ring proton*), 7.56 (d, 1H, *benzene ring proton*), 9.07 (s, 1H, N*H*), 10.10 (s, br, 1H, O*H*). ^{13}C NMR (250 MHz, DMSO-d_6): δ (ppm) 18.8, 21.1, 29.9, 30.1, 34.6, 45.1, 78.5, 79.3, 88.2, 88.9, 105.1, 107.4, 112.6, 113.1, 128.8, 158.7, 159.2, 171.5, 171.7, 201.3, 223.9 (Mn-CO). IR bands (ν): 2021 s and 1934 s (br) (Mn−*CO*), 1654s (br), 1593 m, 1535 m, 1460 w, 1402 w, 1280 m, 1257 s, 1194 w, 1054 m, 904 w, 786 m, 686 m, 613 s cm^{-1}. ESI-MS (negative detection mode): *m*/*z* (%) 508.02 (100) $[M - H]^-$. Anal. Calcd for $C_{23}H_{20}MnNO_9$: C, 54.24; H, 3.96; N, 2.75. Found: C, 53.82; H, 3.97; N, 2.62.

Compound ***16*** *from Me-****4***. To a stirred solution of Me-**4** (50 mg, 0.11 mmol) in a 1/4 (v/v) mixture of H_2O and THF (10 mL) was added solid $LiOH·H_2O$ (184 mg, 4.4 mmol). The mixture was stirred at 45 °C for 14 h. Distilled water (50 mL) was added to the reaction mixture, and this mixture was acidified with 1 M HCl up to pH ∼2 and extracted with EtOAc. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, EtOAc/MeOH/AcOH 20/1/0.075) afforded **16** (14 mg, 41%) as a light yellow solid. Single crystals of **16** were grown by slow evaporation of its $CDCl_3$ solution in a NMR tube. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.14 (s, 3H, CH_3), 1.53 (m, 1H, CH_2), 1.77 (m, 1H, CH_2), 1.99−2.35 (m, 4H, CH_2), 2.47 (m, 1H, CH_2), 2.85 (m, 1H, CH_2), 4.63 (m, 1H, C_5H_3), 5.09 (m, 1H, C_5H_3), 5.17 (m, 1H, C_5H_3), 5.31 (s, br, 1H, N*H*), 5.47 (s, br, 1H, N*H*). ESI-MS (positive detection mode): *m*/*z* (%) 737.00 (80) $[2M + Na]^+$, 396.11 (30) $[M + K]^+$, 380.21 (100) $[M + Na]^+$.

Amide ***18***. The general procedure GP1 was followed: carboxylic acid **9** (1 g, 2.29 mmol), methyl 3-amino-2,4-bis(methoxymethoxy)-benzoate (1.34 g, 4.94 mmol), HATU (1.9 g, 4.94 mmol), DIPEA (637 mg, 4.94 mmol), DMF (10 mL), reaction time 60 h. Flash column chromatography (silica gel, EtOAc/hexanes 1/1 → 1/0) gave **18** as a light brown solid (yield 1.91 g, 71%). Single crystals of **18** were grown by slow evaporation of its solution in a CH_2Cl_2/toluene mixture. R_f = 0.61 (silica gel, EtOAc). ^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 2.79−2.87 (m, 2H, CH_2), 3.06−3.14 (m, 2*H*, CH_2), 3.44 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.84 (s, 3H, $COOCH_3$), 4.99 (s, 2H, OCH_2), 5.00−5.06 (m, 2H, C_5H_4), 5.22 (s, 2H, OCH_2), 5.59−5.64 (m, 2H, C_5H_4), 6.99 (d, 1H, *benzene ring proton*), 7.71 (d, 1H, *benzene ring proton*), 7.82 (s, br, 1H, N*H*). ^{13}C NMR (400 MHz, CD_3CN): δ (ppm) 29.5, 34.3, 52.1, 56.3, 57.2, 84.8, 87.6, 92.1, 94.8, 100.9, 110.6, 119.1, 122.1, 130.5, 155.1, 157.2, 165.9, 171.1, 196.9, 224.1 (Mn−CO); IR bands (ν): 2019 s, 1950 s and 1925 s (Mn−*CO*), 1699 s, 1651 m, 1597 m, 1548 m, 1462 w, 1431 w, 1287 m, 1201 w, 1159 m, 1139 m, 1092 m, 1050 m, 1001 w, 925 m, 855 m, 672 s cm^{-1}. ESI-MS (positive detection mode): *m*/*z* (%) 580.03 (100) $[M + Na]^+$. Anal. Calcd for $C_{24}H_{24}MnNO_{11}$: C, 51.72; H, 4.34; N, 2.51. Found: C, 51.79; H, 4.25; N, 2.45.

Compound ***7***. To a stirred solution of amide **18** (200 mg, 0.36 mmol) in a deoxygenated 4/1 (v/v) mixture of THF and H_2O (30 mL) was added $LiOH·H_2O$ (809.7 mg, 19.75 mmol). The mixture was heated at

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45 °C for 20 h (TLC shows complete ester hydrolysis). The reaction mixture was then evaporated to dryness under vacuum. Degassed 4 N HCl in dioxane was then added slowly to adjust the pH of the reaction mixture close to zero. The mixture was then stirred at room temperature. After 15 min the reaction was completed (checked by TLC), and brine (50 mL) was added to the mixture, which was then extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with distilled water (5 × 50 mL) and brine (2 × 25 mL), dried over anhydrous Na_2SO_4, and filtered. Removal of the solvent followed by flash column chromatography (silica gel, EtOAc/MeOH/AcOH 1/:0/0 → 20/1/0.2) yielded compound **7** as a light brown solid (115 mg, 70%). R_f = 0.75 (silica gel, EtOAc/MeOH/AcOH 20/1/0.5). ^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 2.79−2.87 (m, 2H, CH_2), 3.06−3.14 (m, 2H, CH_2), 5.00−5.06 (m, 2H, C_5H_4), 5.59−5.64 (m, 2H, C_5H_4), 6.46 (d, 1H, *benzene ring proton*), 7.63 (d, 1H, *benzene ring proton*), 7.47 (s, br, 1H, N*H*). ^{13}C NMR (250 MHz, pyridine-d_5): δ (ppm) 32.2, 37.5, 87.1, 90.2, 94.8, 109.7, 112.2, 117.4, 131.9, 160.5, 160.7, 175.7, 177.2, 198.9, 226.5 (Mn−*CO*). IR bands (ν): 2948 w, 2024 s, 1924 s (br) (Mn−*CO*), 1670 m, 1635 m, 1596 m, 1540 m, 1461 w, 1378w, 1291 s, 1155 w, 1084 m, 915 w, 728 w cm^{-1}. ESI-MS (negative detection mode): m/z (%) 453.95 (100) $[M - H]^-$. Anal. Calcd for $C_{19}H_{14}MnNO_9$: C, 50.13; H, 3.10; N, 3.08. Found: C, 49.82; H, 3.45; N, 2.85.

Compound ***8***. To a solution of **7** (350 mg, 0.875 mmol) in benzene (10 mL) and AcOH (3 mL) was added 10 g of freshly prepared Zn(Hg), followed by the addition of distilled H_2O (5 mL) and of concentrated HCl (7 mL). The mixture was deoxygenated by bubbling N_2 for 10 min and heated at 90 °C for 12 h. The reaction mixture was then filtered, diluted with distilled water (100 mL), and extracted with EtOAc (3 × 50 mL). The organic phase was washed several times with water and finally with brine, dried over anhydrous Na_2SO_4, and filtered. Removal of the solvent followed by flash column chromatography (silica gel, EtOAc/MeOH/AcOH 20/1/0.1) yielded compound **8** as a light brown solid (216 mg, 64%). R_f = 0.44 (silica gel, EtOAc/MeOH/AcOH 20/1/0.1). ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.62−1.90 (m, 2H, CH_2), 2.15−2.43 (m, 4H, 2 × CH_2), 4.91 (s, br, 2H, C_5H_4), 4.99 (s, br, 2H, C_5H_4), 6.46 (s, br, 1H, *benzene ring proton*), 7.59 (s, br, 1H, *benzene ring proton*), 9.05 (s, br, 1H, N*H*). ^{13}C NMR (250 MHz, DMSO-d_6): δ (ppm) 26.3 (min) and 27.3 (maj) (rotamers, 2 × CH_2), 33.6 (min) and 35.1 (maj) (rotamers, CH_2), 83.1 (C_5H_4), 83.6 (C_5H_4), 83.7 (C_5H_4), 104.5 (min) and 107.6 (maj) (rotamers, *benzene ring carbon*), 105.1 (min) and 108.1 (maj) (rotamers, *benzene ring carbon*), 113.2 (*benzene ring carbon*), 129.5 (*benzene ring carbon*), 159.6 (2 × *benzene ring carbon*), 172.2 (*C*OOH), 174.9 (*C*ONH), 226.1 (Mn−*CO*); IR bands (ν): 2019 s and 1921 s (Mn−*CO*), 1634 s (br, *C*OOH, *C*ONH) cm^{-1}. ESI-MS (negative detection mode): m/z (%) 439.80 (100) $[M - H]^-$.

Compound ***20***. 2-Methyl-1-tetralone (**19**; 320 mg, 2 mmol) and $Cr(CO)_6$ (572 mg, 2.6 mmol) in a degassed 9/1 (v/v) mixture of Bu_2O/THF (30 mL) was heated for 36 h at 140 °C under an N_2 atmosphere in the dark. The mixture was then cooled to room temperature, filtered, and concentrated. Flash column chromatography (silica gel, hexane/EtOAc 4/1 → 3/1) yielded a diasteriomeric mixture of **20** (360 mg, 61%) as an orange-yellow solid. The characterization data matched well with those reported earlier.[38]

tert-Butyl Ester ***21***. To a stirred solution of **20** (150 mg, 0.52 mmol) in a 1/1 (v/v) mixture of ^{t}BuOH and Et_2O (6 mL) was added ^{t}BuOK (116 mg, 1.03 mmol) at 0 °C under an N_2 atmosphere. After 20 min, *tert*-butyl acrylate (666 mg, 5.2 mmol) was added to the reaction mixture, and this mixture was stirred for 2.5 h at 0 °C. The reaction was quenched with saturated NH_4Cl, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and filtered. The solvent and *tert*-butyl acrylate were removed using a high-vacuum pump. Flash column chromatography (silica gel, hexane/EtOAc 4/1) gave **21** as an orange oil (170 mg, 79%). R_f = 0.2 (silica gel, hexane/EtOAc 5/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.22 (s, 3H, CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 1.66−1.79 (m, 1H, CH_2), 1.85−2.09 (m, 3H, CH_2), 2.14−2.31(m, 2H, CH_2), 2.53−2.69 (m, 1H, CH_2), 3.04−3.20 (m, 1H, CH_2), 5.15 (d, 1H, *benzene ring proton*), 5.32 (m, 1H, *benzene ring proton*), 5.60 (m, 1H, *benzene ring proton*), 6.15 (d, 1H, *benzene ring proton*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) 22.1, 24.3, 28.1, 29.8, 29.9, 33.6, 43.9, 80.6, 89.6, 90.1, 91.8, 92, 94.5, 113.8, 172.5, 199.7, 230.9 (Cr-CO); IR bands (ν): 2976 w, 2933 w, 1964 s (Cr−CO), 1877s (Cr−CO), 1721 s, 1678 m, 1451 w, 1366 w, 1307 m, 1254 w, 1222 m, 1148 s, 894 w, 654 s, 616 s cm^{-1}. ESI-MS (positive detection mode): m/z (%) 462.86 (30) $[M + K]^+$, 446.91 (50) $[M + Na]^+$, 424.93 (20) $[M + H]^+$, 368.91 (100) $[M - 2CO + H]^+$.

Compound ***22***. To a stirred solution of **21** (150 mg, 0.35 mmol) in a 3/1 (v/v) mixture of MeOH and THF (12 mL) was added 1 M aqueous NaOH (4.2 mL). The mixture was deoxygenated by bubbling N_2 for 10 min and stirred for 14 h at room temperature. The reaction mixture was then diluted with distilled water (50 mL), and the aqueous layer was washed with Et_2O (2 × 30 mL). The aqueous layer was acidified with 1 M HCl up to pH ∼2 and extracted with EtOAc (2 × 30 mL). The combined organic phase was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The carboxylic acid **22** was obtained as an orange sticky solid (112 mg, 87%) which was used for the next step without further purification. For analytical purposes, **22** was recrystallized by slow evaporation of its Et_2O/EtOAc solution. R_f = 0.4 (silica gel, EtOAc). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.26 (s, 3H, CH_3), 1.70−2.17 (m, 4H, CH_2), 2.29−2.49 (m, 2H, CH_2), 2.58−2.74 (m, 1H, CH_2), 3.02−3.20 (m, 1H, CH_2), 5.16 (d, 1H, *benzene ring proton*), 5.32 (m, 1H, *benzene ring proton*), 5.60 (m, 1H, *benzene ring proton*), 6.15 (d, 1H, *benzene ring proton*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) 22.1, 24.3, 28.6, 29.8, 33.6, 43.9, 89.6, 90.1, 91.5, 92.1, 94.5, 113.8, 178.9, 199.7, 230.9 (Cr-CO). IR bands(ν): 3085 w, 2931 w, 1962 s, 1871 s, 1704 s, 1676 s, 1522 w, 1431 m (br), 1285 w, 1222 m, 1044 w, 1008 w, 832 w, 654 s, 614 s cm^{-1}. ESI-MS (negative detection mode): m/z (%) 735.14 (100) $[2M - H]^-$. Anal. Calcd for $C_{17}H_{16}CrO_6 \cdot 0.5Et_2O$: C, 56.29; H, 5.22. Found: C, 56.27; H, 4.74.

Compound ***23***. The general procedure GP1 was followed: carboxylic acid **22** (200 mg, 0.54 mmol), 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate (434 mg, 1.63 mmol), HATU (523 mg, 1.63 mmol), DIPEA (211 mg, 1.63 mmol), DMF (6 mL, deoxygenated previously by bubbling N_2), reaction time 20 h. On flash column chromatography (silica gel, hexane/EtOAc 3/1), **23** was obtained as an orange oil which solidified slowly when coevaporated with pentane (161 mg, 48%). R_f = 0.2 (silica gel, EtOAc/hexanes 1/3). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 0.10 (s, 9H, $Si(CH_3)_3$), 1.15 (m, 2H, CH_2−CH_2-$Si(CH_3)_3$), 1.29 (s, 3H, CH_3), 1.82−2.04 (m, 2H, CH_2), 2.06−2.25 (m, 2H, CH_2), 2.44−2.74 (m, 3H, CH_2), 3.02−3.22 (m, 1H, CH_2), 4.45 (m, 2H, CH_2−CH_2−$Si(CH_3)_3$), 5.16 (d, 1H, *benzene ring proton*), 5.32 (m, 1H, *benzene ring proton*), 5.60 (m, 1H, *benzene ring proton*), 6.15 (d, 1H, *benzene ring proton*), 6.51 (d, 1H, *benzene ring proton*), 7.58 (d, 1H, *benzene ring proton*), 7.97 (s, 1H, N*H*), 10.79 (s, br, 1H, O*H*), 11.87 (s, 1H, O*H*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) −1.46, 17.4, 22.4, 24.3, 30.6, 31.2, 34.1, 44.1, 63.9, 89.6, 90.1, 91.5, 92.1, 94.5, 104.5, 111.1, 113.8, 114.1, 127.6, 153.8, 154.6, 170.4, 173.1, 199.9, 230.8 (Cr−CO). IR bands (ν): 2954 w, 1968 s (Cr−*CO*), 1885 (Cr−*CO*), 1654 s (br), 1595 w, 1524 m, 1452 w, 1386 w, 1288 w, 1217 s, 1145 m, 1061 w, 931 w, 857 s, 787 w, 752 s, 654 s cm^{-1}. ESI-MS (positive detection mode): m/z (%) 641.96 (20) $[M + Na]^+$, 310.03 (100) $[M + H]^{2+}$.

Compound ***5***. To a stirred solution of amide **23** (300 mg, 0.48 mmol) in DMF (5 mL) was added tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF; 267 mg, 0.97 mmol) at room temperature, and the mixture was heated at 40 °C for 40 min. The reaction mixture was then cooled to room temperature, brine was added, and this mixture was extracted with EtOAc (3 × 50 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, EtOAc/MeOH/AcOH 20/1/0.05) of the resulting residue gave compound **5** (215 mg, 85%) as an orange powder. R_f = 0.43 (silica gel, EtOAc/MeOH/AcOH 20/1/0.05). ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.16 (s, 3H, CH_3), 1.71−1.92 (m, 3H, CH_2), 1.96−2.11 (m, 1H, CH_2), 2.19−2.65 (m, 3H, CH_2), 3.02−3.24 (m, 1H, CH_2), 5.72 (m, 2H, *benzene ring proton*), 6.08 (m, 1H, *benzene ring proton*), 6.23 (m, 1H, *benzene ring proton*), 6.39 (d, 1H, *benzene ring proton*), 7.54 (d, 1H, *benzene ring proton*), 9.08 (s, 1H, N*H*), 10.10

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(s, br, 1H, O*H*). ^{13}C NMR (250 MHz, DMSO-d_6): δ (ppm) 22.4, 24.2, 30.3, 30.6, 33.1, 44.4, 92.6, 93.1, 93.2, 93.6, 97.9, 105.7, 107.8, 113.2, 116.9, 129.3, 158.9, 159.6, 172.2, 172.6, 200.5, 232.5 (Cr−*C*O). IR bands (ν): 3376 w, 2932 w, 1962 s (Cr−*C*O), 1886 s (Cr−*C*O), 1666 m, 1633 m (br), 1628 m, 1436 w, 1378 w, 1274 m, 1188 w, 1160 w, 1004 w, 1059 w, 822 w, 655 s, 617 s cm^{-1}. ESI-MS negative detection mode): m/z (%) 517.88 (100) $[M - H]^-$. Anal. Calcd for $C_{24}H_{21}CrNO_9$: C, 55.50; H, 4.08; N, 2.70. Found: C, 55.23; H, 3.95; N, 2.57.

Compound ***25***. To a solution of [3]-ferrocenophanone (**24**; 225 mg, 0.94 mmol) in 12 mL of THF was added 0.5 M KHMDS in toluene (3 mL, 1.5 mmol) slowly at −78 °C. The mixture was stirred for 30 min, and HMPA (2 mL) and MeI (1.3 g, 9.4 mmol) were added sequentially. After 3 h at −78 °C, the reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution and extracted with Et_2O (3 × 30 mL). The organic phase was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Flash column chromatography (silica gel, hexane/EtOAc 5/1) gave **25** as an orange solid (first orange band, 113 mg, 67% based on the starting material consumed) together with 90 mg of the unreacted **24** (2nd orange band). R_f = 0.44 (silica gel, hexane/EtOAc 5/1). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.11 (d, 3H, C*H*$_3$), 2.64−2.95 (m, 2H, C*H*$_2$), 3.72−3.90 (m, 1H, C*H*), 3.94−3.98 (m, 1*H*, C$_5$*H*$_4$), 4.10−4.15 (m, 1H, C$_5$*H*$_4$), 4.32−4.37 (m, 1H, C$_5$*H*$_4$), 4.39−4.37 (m, 2H, C$_5$*H*$_4$), 4.63−4.68 (m, 1H, C$_5$*H*$_4$), 4.72−4.76 (m, 1H, C$_5$*H*$_4$), 5.06−5.10 (m, 1H, C$_5$*H*$_4$). ^{13}C NMR (200 MHz, $CDCl_3$): δ (ppm) 15.4, 40.1, 46.1, 66.3, 68.1, 69.8, 70.3, 72.1, 72.3, 72.7, 73.5, 74.9, 85.9, 213.9. IR bands (ν): 3082 w, 2973 w, 2931 w, 2845 w, 1733 w, 1675 s, 1438 m, 1366 w, 1181 m, 1048 w, 1036 s, 973 w, 901 w, 847 m, 827 s, 754 w, 641 w cm^{-1}. ESI-MS (positive detection mode): m/z (%) 253.88 (100) $[M]^+$. Anal. Calcd for $C_{14}H_{14}FeO$: C, 66.17; H, 5.55. Found: C, 66.05; H, 5.78.

Compound ***26***. To a stirred solution of **25** (130 mg, 0.51 mmol) in a 1/1 (v/v) mixture of ^{t}BuOH and Et_2O (6 mL) was added ^{t}BuOK (85 mg, 0.75 mmol) slowly at room temperature under an N_2 atmosphere. After 15 min, *tert*-butyl acrylate (326 mg, 2.5 mmol) was added. After 6 h at room temperature TLC (silica gel, hexane/EtOAc 4/1) showed no more starting ketone present. The reaction mixture was quenched by adding 20 mL of 0.5 M HCl and extracted with 40 mL of EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and dried under vacuum (to remove the excess *tert*-butyl acrylate). Flash column chromatography was performed on silica gel. The first orange band was eluted using an EtOAc/hexanes mixture (1/6, v/v) and was isolated as **26** (127 mg, 65%). The second orange band was eluted using an EtOAc/MeOH/AcOH mixture (20/1/0.05, v/v) and was isolated as the carboxylic acid **27** (trace amount, the longer reaction time increases the amount of carboxylic acid **27** formed). R_f = 0.35 (silica gel, hexane/EtOAc 5/1). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 3H, C*H*$_3$), 1.50 (s, 9H, C(C*H*$_3$)$_3$), 1.76−1.93 (m, 1H, C*H*$_2$), 2.11−2.44 (m, 2H, C*H*$_2$), 2.79 (s, 2H, C*H*$_2$), 3.06−3.15 (m, 1H, C*H*$_2$), 4.05 (s, br, 1H, C$_5$*H*$_4$), 4.11 (s, br, 1H, C$_5$*H*$_4$), 4.33 (s, br, 2H, C$_5$*H*$_4$), 4.42 (s, br, 1H, C$_5$*H*$_4$), 4.54 (s, br, 1H, C$_5$*H*$_4$), 4.64 (s, br, 1H, C$_5$*H*$_4$), 4.91 (s, br, 1H, C$_5$*H*$_4$). ^{13}C NMR (200 MHz, $CDCl_3$): δ (ppm) 22.2, 28.1, 31.5, 32.4, 44.3, 54.8, 69.2, 69.9, 70.3, 71.7, 72.0, 72.1, 72.2, 72.4, 75.8, 80.6, 82.9, 173.1, 213.7. IR bands (ν): 2971 w, 2927, 1721 s, 1652 s, 1456 w, 1377 m, 1336 w, 1303 m, 1244 w, 1146 s, 1057 m, 1032 m, 935 w, 854 m, 836 m, 759 m cm^{-1}. ESI-MS (positive detection mode): m/z (%) 326.92 (100) $[M - 2CO + H]^+$, 382.93 (50) $[M + H]^+$. Anal. Calcd for $C_{21}H_{26}FeO_3$: C, 65.98; H, 6.86. Found: C, 66.27; H, 6.94.

Compound ***27***. To a stirred solution of **26** (80 mg, 0.2 mmol) in CH_2Cl_2 (6 mL) was added Me_3SiI (0.054 mL, 0.4 mmol) dropwise at 0 °C under an N_2 atmosphere. The mixture was stirred at room temperature for 2 h. The reaction mixture was then poured into 30 mL of distilled water and was extracted with EtOAc (2 × 30 mL). The combined organic phase was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed. Flash column chromatography (silica gel, EtOAc/MeOH/AcOH 20/1/0.05) afforded **27** as a yellow solid (56 mg, 82%). R_f = 0.41 (silica gel, EtOAc). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.35 (s, 3H, C*H*$_3$), 1.76−1.90 (m, 1H, C*H*$_2$), 2.02−2.18 (m, 1H, C*H*$_2$), 2.25−2.41 (m, 1H, C*H*$_2$), 2.66−2.86 (m, 3H, C*H*$_2$), 4.08 (s, br, 1H, C$_5$*H*$_4$), 4.13 (s, br, 1H, C$_5$*H*$_4$), 4.36 (s, br, 2H, C$_5$*H*$_4$), 4.54 (s, br, 2H, C$_5$*H*$_4$), 4.64 (s, br, 1H, C$_5$*H*$_4$), 4.78 (s, br, 1H, C$_5$*H*$_4$), 12.32 (s, br, 1H, COO*H*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) 21.9, 30.3, 33.1, 69.7, 70.4, 70.5, 71.5, 71.8, 72.1, 72.4, 72.7, 76.4, 83.2, 213.3 (signal for COOH is not visible). IR bands (ν): 2920 w, 1699 s, 1649 s, 1438 w, 1409 w, 1312 m, 1245 w, 1217 s, 1056 w, 1038 w, 955 m, 854 m, 766 w, 676 w, 638 w cm^{-1}. ESI-MS (positive detection mode): m/z (%) 326.04 (100) $[M]^+$. Anal. Calcd for $C_{17}H_{18}FeO_3 \cdot 0.5H_2O$: C, 60.89; H, 5.71. Found: C, 60.97; H, 5.76.

Compound ***28***. The general procedure GP1 was followed: carboxylic acid **27** (600 mg, 1.8 mmol), methyl 3-amino-2,4-dimethoxybenzoate (777 mg, 3.7 mmol), HATU (1.2 g, 3.7 mmol), DIPEA (477 mg, 3.7 mmol), DMF (10 mL), reaction time 24 h. Flash column chromatography (silica gel, hexane/EtOAc 1/1 → 0/1) gave **28** as an orange sticky solid (550 mg, 57%). R_f = 0.11 (silica gel, hexane/EtOAc 1/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.46 (s, 3H, C*H*$_3$), 1.91−2.05 (m, 1H, C*H*$_2$), 2.19−2.35 (m, 1H, C*H*$_2$), 2.40−2.59 (m, 1H, C*H*$_2$), 2.81 (s, 2H, C*H*$_2$), 3.11−3.25 (m, 1H, C*H*$_2$), 3.86 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 4.05 (m, 1H, C$_5$*H*$_4$), 4.09 (m, 1H, C$_5$*H*$_4$), 4.32 (m, 2H, C$_5$*H*$_4$), 4.43 (m, 1H, C$_5$*H*$_4$), 4.56 (m, 1H, C$_5$*H*$_4$), 4.67 (m, 1H, C$_5$*H*$_4$), 4.96 (m, 1H, C$_5$*H*$_4$), 6.75 (d, 1H, *benzene ring proton*), 7.02 (s, br, 1H, N*H*), 6.85 (d, 1H, *benzene ring proton*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) 22.1, 33.1, 33.2, 44.5, 52.1, 55.1, 56.2, 62.1, 69.3, 70.1, 71.7, 71.8, 72.1, 72.3, 72.4, 75.8, 77.2, 82.9, 106.7, 117.1, 120.2, 131.5, 157.5, 159.1, 165.6, 172.4, 214.1. IR bands (ν): 2963 w, 2360 w, 1720 w, 1655 s (br), 1594 m, 1496 w, 1414 w, 1261 s, 1215 w, 1096 s, 1056 m, 1016 s, 795 w, 726 s cm^{-1}. ESI-MS (positive detection mode): m/z (%) 519.01 (80) $[M]^+$, 541.94 (100) $[M + Na]^+$.

Compound ***29***. The general procedure GP1 was followed: carboxylic acid **27** (150 mg, 0.46 mmol), methyl 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate (309 mg, 1.1 mmol), HATU (443 mg, 1.38 mmol), DIPEA (178 mg, 1.38 mmol), DMF (5 mL), reaction time 20 h. Flash column chromatography (silica gel, hexane/EtOAc 2.5/1) gave **29** as an orange sticky solid (170 mg, 64%). Single crystals for X-ray diffraction were grown from a CH_2Cl_2/pentane mixture at 0 °C. R_f = 0.48 (silica gel, hexane/EtOAc 2/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 0.09 (s, 9H, Si(C*H*$_3$)$_3$), 1.15 (m, 2H, CH$_2$−C*H*$_2$−Si(CH$_3$)$_3$), 1.59 (s, 3H, C*H*$_3$), 1.84−2.01 (m, 1H, C*H*$_2$), 2.42−2.66 (m, 2H, C*H*$_2$), 2.80−3.02 (m, 3H, C*H*$_2$ and C*H*$_2$ of ferrocenophanone), 4.09 (m, 2H, C$_5$*H*$_4$), 4.35 (m, 2H, C$_5$*H*$_4$), 4.40−4.44 (m, 2H, C$_5$*H*$_4$), 4.49 (m, 2H, C*H*$_2$-CH$_2$− Si(CH$_3$)$_3$), 4.76 (m, 1H, C$_5$*H*$_4$), 4.84 (m, 1H, C$_5$*H*$_4$), 6.53 (d, 1H, *benzene ring proton*), 7.85 (d, 1H, *benzene ring proton*), 8.09 (s, br, 1H, N*H*), 11.10 (s, 1H, O*H*), 11.88 (s, 1H, O*H*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) −1.4, 17.3, 21.6, 32.9, 34.1, 44.6, 54.6, 63.8, 69.8, 69.9, 70.7, 71.4, 72.1, 72.2, 72.3, 72.4, 75.5, 82.5, 104.6, 111.1, 114.3, 127.4, 153.8, 154.4, 170.5, 173.3, 213.3. IR bands (ν): 2950 w, 1653 s (br), 1595 w, 1533 m, 1385 s, 1330 s, 1292 w, 1256 s, 1218 m, 1146 s, 1057 s, 1032 w, 857 s, 836 s, 787 s, 636 w cm^{-1}. ESI-MS (positive detection mode): m/z (%) 577.07 (70) $[M]^+$, 600.03 (100) $[M + Na]^+$. Anal. Calcd for $C_{29}H_{35}FeNO_6Si$: C, 60.31; H, 6.11; N, 2.43. Found: C, 60.45; H, 6.25; N, 2.16.

Compound ***6*** *from Amide* ***28***. To a stirred solution of the amide **28** (240 mg, 0.46 mmol) in $CHCl_3$ (8 mL) was added BBr_3 (0.42 mL, 4.6 mmol) at −78 °C (just before the solution freezes) under an N_2 atmosphere. The gray mixture was stirred for 18 h at room temperature. The reaction mixture was poured into distilled water (20 mL) and extracted with EtOAc (3 × 25 mL) and washed with brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column chromatography on silica gel (pure EtOAc → EtOAc/MeOH/AcOH 20/1/0.07) gave **Me-6** (90 mg, yellow sticky solid), followed by **6** (70 mg, yellow powder).

To a stirred solution of **Me-6** (90 mg, 0.18 mmol) in a 1/3 (v/v) mixture of THF and MeOH (8 mL) was added a 1 M NaOH solution (5.4 mL), and this mixture was deoxygenated by bubbling N_2 for 15 min. The mixture was heated at 60 °C for 16 h under an N_2 atmosphere, diluted with distilled water (50 mL), acidified with 1 M HCl up to pH ∼2, and extracted with EtOAc. The organic phase was

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dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, EtOAc/MeOH/AcOH 20/1/0.07) afforded **6** (25 mg). Combined yield of **6** : 95 mg (43%).

*Compound **6** from Amide **29**.* To a stirred solution of amide **29** (100 mg, 0.17 mmol) in DMF (5 mL) was added tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF; 117 mg, 0.42 mmol) at room temperature, and the mixture was heated at 40 °C for 1 h. The reaction mixture was then cooled to room temperature, brine was added, and this mixture was extracted with EtOAc (3 × 50 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, EtOAc/MeOH/AcOH 20/1/0.07) of the resulting residue gave compound **6** (64 mg, 78%) as a yellow powder. R_f = 0.33 (silica gel, EtOAc/MeOH/AcOH 20/1/0.07). ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.32 (s, 3H, CH_3), 1.93−2.03 (m, 1H, CH_2), 2.11−2.28 (m, 1H, CH_2), 2.46−2.62 (m, 1H, CH_2), 2.76 (s, 2H, CH_2), 2.97−3.15 (m, 1H, CH_2), 4.07 (m, 1H, C_5H_4), 4.16 (m, 1H, C_5H_4), 4.37 (m, 2H, C_5H_4), 4.52 (m, 1H, C_5H_4), 4.59 (m, 2H, C_5H_4), 5.06 (m, 1H, C_5H_4), 6.45 (d, 1H, *benzene ring proton*), 7.59 (d, 1H, *benzene ring proton*), 9.10 (s, 1H, N*H*), 10.22 (s, br, 1H, O*H*). ^{13}C NMR (250 MHz, DMSO-d_6): δ (ppm) 22.6, 31.5, 32.6, 43.5, 55.2, 69.3, 69.4, 70.7, 71.6, 72.1, 72.4, 72.7, 72.8, 76.6, 83.3, 105.1, 108.2, 113.4, 129.3, 159.5, 159.6, 172.3, 172.7, 213.4. IR bands (ν): 3373 m, 2924 w, 2585 w, 1654 s (br), 1620 m, 1597 s, 1529 s, 1385 m, 1276 m, 1234 m, 1281 m, 1160 m, 1060 s, 1037 w, 950 w, 786 s, 624 w cm^{-1}. ESI-MS (positive detection mode): *m*/*z* (%) 477.02 (100) $[M]^+$, 499.97 (50) $[M + Na]^+$. Anal. Calcd for $C_{24}H_{23}FeNO_6 \cdot 0.5H_2O$: C, 59.25;, H, 4.97; N, 2.88. Found: C, 59.09; H, 5.00; N, 2.69.

*Compound **31**.* The general procedure GP1 was followed: carboxylic acid **30** (95 mg, 0.29 mmol), methyl 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate (150 mg, 0.56 mmol), HATU (180 mg, 0.56 mmol), DIPEA (72 mg, 0.56 mmol), DMF (6 mL), reaction time 20 h. Flash column chromatography (silica gel, hexane/EtOAc 2.5/1) gave **31** as a red sticky solid (78 mg, 47%). R_f = 0.35 (silica gel, hexane/EtOAc 2.5/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 0.09 (s, 9H, $Si(CH_3)_3$), 1.16 (m, 2H, $CH_2-CH_2-Si(CH_3)_3$), 1.39 (s, 3H, CH_3), 1.71−2.18 (m, 3H, CH_2), 2.21−2.78 (m, 5H, CH_2), 4.21 (s, 5H, C_5H_5), 4.48 (m, 4H, 2H from C_5H_4 and $CH_2-CH_2-Si(CH_3)_3$), 4.83 (m, 1H, C_5H_4), 6.43 (d, 1H, *benzene ring proton*), 7.75 (d, 1H, *benzene ring proton*), 7.99 (s, br, 1H, N*H*), 10.90 (s, 1H, O*H*), 11.88 (s, 1H, O*H*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) −0.1, 18.3, 21.9, 23.8, 31.8, 33.2, 38.9, 46.8, 65.2, 67.7, 71.5, 71.6, 72.7, 75.6, 92.3, 105.8, 112.5, 115.6, 128.4, 155.3, 156.1, 171.9, 175.1, 209.8. IR bands (ν): 2953 w, 1653 s (br), 1595 w, 1529 m, 1438 w, 1385 s, 1250 s, 1216 m, 1145 s, 1061 m, 1001 m, 931 w, 834 s, 787 s, 693 m cm^{-1}. ESI-MS (positive detection mode): *m*/*z* (%) 591.04 (100) $[M]^+$, 613.95 (20) $[M + Na]^+$.

■ ASSOCIATED CONTENT

Supporting Information

Figures, tables, and CIF files giving ^{1}H and ^{13}C NMR spectra, hydrogen-bonding interactions in the single-crystal structures of **4**, **16**, and **18**, X-ray crystallographic data for compounds **4**, **16**, **18**, and **29**, and the dependence of HepG2 cell mass (%) with increasing concentrations of compounds. This material is available free of charge via the Internet at http://pubs.acs.org. Crystal structure data are also deposited at the Cambridge Structural Database (CCDC numbers: **4**, 823234; **16**, 823236; **18**, 823235; **29**, 823233).

■ AUTHOR INFORMATION

Corresponding Author

*Fax: 0234 32-14378. E-mail: Nils.Metzler-Nolte@rub.de.

Notes

The authors declare no competing financial interest.

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