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Syntheses and Antibacterial Properties of *iso*-Platencin, Cl-*iso*-Platencin and Cl-Platencin: Identification of a New Lead Structure

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Abstract: Platencin is a novel antibiotic which is active against multiresistant pathogens. We describe efficient syntheses of three platencin analogues of varying activities which allow further conclusions about the pharmacophoric part of the molecule. The unnatural antibiotic *iso*-platencin, which is about as active as natural platencin, but much more selective, was identified as a new lead structure.

Keywords: antibiotics · natural products · stereoselectivity · terpenoids · total synthesis

The rise of multiresistant bacteria is a serious and urgent threat, especially in hospitals, where antibiotics are permanently used and bacteria strains easily evolve that withstand multiple antibiotic classes. Infections by Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE) and penicillin-resistant *Streptococcus pneumonia* (PRSP) are particularly worrying.[1] From these observations the urgency to develop new antibiotics is obvious. Since novel antibiotics usually address well-known targets just at different binding sites or through new binding modes, the discovery of platencin[2] (**1**, Figure 1) and platensimycin[3] (**2**), has been hailed as a breakthrough in antibiotics research.

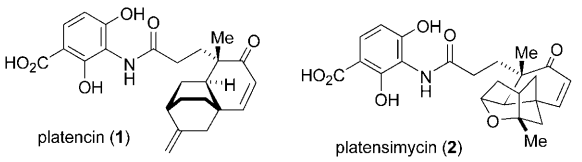

Figure 1. Structures of platencin (**1**) and platensimycin (**2**).

This is due to the fact that compounds **1** and **2** address an apparently ideal biological target. They are the first potent inhibitors of bacterial fatty acid biosynthesis (Fab), which is essential to the survival of the pathogens, distinct from the mammalian pathway and generally highly conserved among bacteria. While platensimycin is blocking the fatty acid condensing enzyme FabF selectively, platencin inhibits the enzymes FabF and FabH. Both compounds thus display a broad-spectrum antibiotic activity against many drug-resistant pathogens such as methycillin-, macrolide- and linezolid-resistant *S. aureus*, vancomycin intermediate *S. aureus*, vancomycin-resistant *enterococci*, and *Streptococcus pneumoniae*.[2] Owing to the unique mode of action, no cross-resistances to existing drugs have been observed so far. In addition the toxicity profile seems to be good. However, the in vivo efficacy is low, due to the limited metabolic stability, so that suitable synthetic derivatives will have to be prepared and investigated to find more promising drug candidates.[1]

Not surprisingly numerous synthetic approaches to platencin[4] and platensimycin[5] have been uncovered. Meanwhile also platensimycin B_1–B_4, platensimide A, homoplatensimide A, platensic acid and its methyl ester, platencin A_1 and platensimycin A_1, which are all much less biologically active or even inactive natural derivatives of platensimycin, have been discovered.[6] In addition several analogues of platensimycin with moderate to no biological activity have been reported.[7] From these observations a simple guideline to the platensimycin pharmacophore was delineated.[7c] Modifications on the aromatic part heavily impact the biological profile. The removal of the carboxylic acid or one of the two hydroxy groups renders the molecule inactive. On the other hand modifications in the eastern part are more tolerated. But so far no modification has resulted in a comparable or even better biological activity than the parent structure platensimycin. As the only example of a platencin-derivative, (−)-nor-platencin was published recently[8] and

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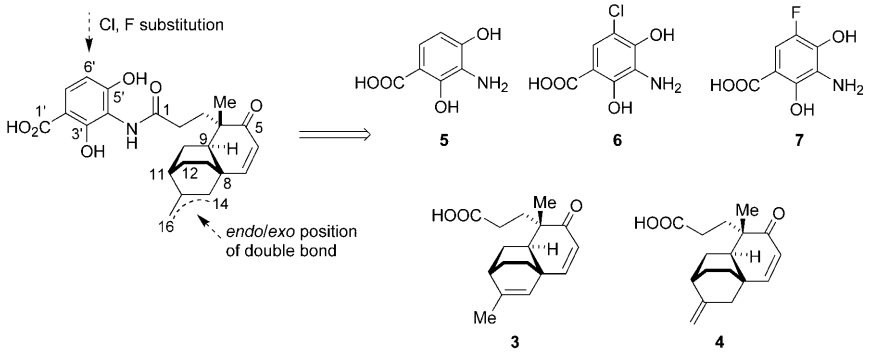
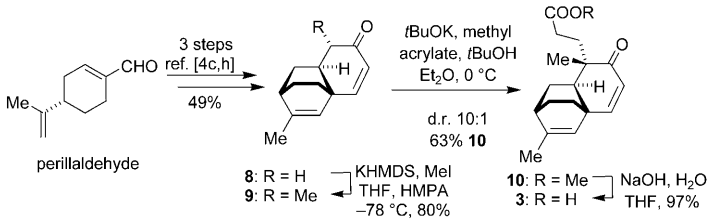
showed moderate antibiotic activity (4–16 times less potent than platencin).

Our goal was to synthesize new platencin derivatives to shed further light on the structure–activity relationship. Specifically the influence of the double bond position (natural *exo* position C15–C16 vs *endo* position C14–C15, Scheme 1) and the introduction of a halogen substituent on the C6′ position were investigated. The idea behind introducing an inert substituent on C6′ was to improve the stability of the aromatic system towards oxidation to the *p*-quinoid system.



Scheme 1. Envisaged sites of derivatization on platencin and required fragments.

The synthesis of *iso*-platensic acid (**3**) relies on our short synthesis of platencin[4c,h] which delivers tricycle **8** in only three steps and high yield (49%, Scheme 2). After methylation, the side chain was introduced via 1,4-addition to methyl acrylate. Surprisingly the subtle changes caused by the alkene *endo*-position led to an excellent 10:1 diastereoselectivity of this addition compared to the moderate 4:1 ratio[4h] in the case of the regular platencin core. Saponification of the methyl ester yielded *iso*-platensic acid (**3**).

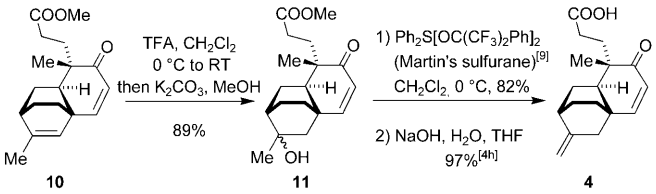


Scheme 2. Synthesis of *iso*-platensic acid **3**.

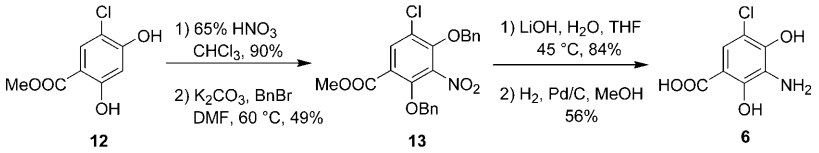
Encouraged by the improved 1,4-addition selectivity we investigated the possibility to convert *iso*-platensic acid methyl ester (**10**) to platensic acid (**4**, Scheme 3). Indeed the transposition of the *endo*-alkene to the *exo*-position worked well under the conditions[4h] developed earlier for substrate **8** and after saponification platensic acid (**4**) was obtained in good overall yield.

Having secured practical routes to *iso*-platensic acid (**3**) as well as to **4**, we turned our attention to the western aromatic units. The synthesis of the Cl-substituted amino acid **6** (Scheme 4) started from known methyl 5-chloro-2,4-dihydroxybenzoate[10] (**12**) which was nitrated with 65% HNO_3 in excellent yield and protected as bis-benzyl ether to furnish compound **13**. Saponification of the methyl ester, followed by concomitant reduction of the nitro group and bis-debenzylation, delivered the Cl-western unit **6**.

The analogous synthesis of the F derivative was hampered by the fact that several attempts to introduce fluorine in methyl



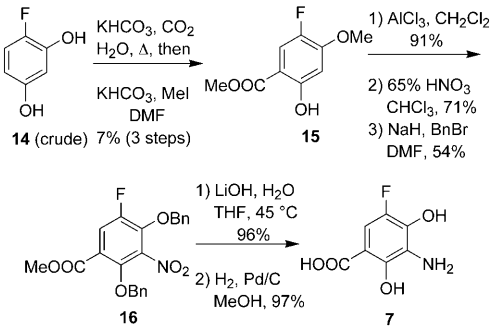
Scheme 3. Conversion of *iso*-platensic acid methyl ester **10** to platensic acid **4**.



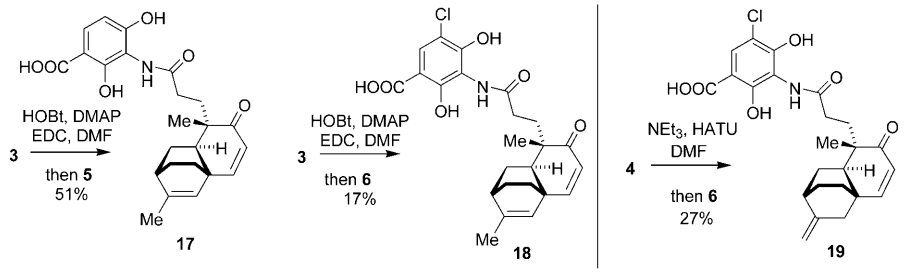
Scheme 4. Synthesis of Cl-western unit **6**.

2,4-dihydroxybenzoate failed. We therefore turned to the known[11] introduction of fluorine into the more electron rich resorcin core. The resulting crude mixture of fluorinated resorcin compounds was subjected to a Kolbe–Schmitt reaction[12] and a subsequent double methylation delivered compound **15** (Scheme 5) in low but sufficient yield. Selective demethylation with Lewis acid, followed by nitration and bis-benzylation gave intermediate **16** which was processed to the F-western unit **7** in the same way as the Cl-derivative **13**.

With all required fragments in hand, only coupling via amidation was left. *iso*-Platencin (**17**, Scheme 6) was obtained from *iso*-platensic acid (**3**) and known[5p] amino acid **5** via optimized coupling conditions (HOBt, DMAP, EDC, DMF) in 51% yield. For obtaining a clean product, an aqueous workup and the use of EDC instead of DCC proved essential. Coupling of *iso*-platensic acid (**3**) with Cl-western



Scheme 5. Synthesis of F-western unit **7**.



Scheme 6. Syntheses of *iso*-platencin (**17**), Cl- *iso*-platencin (**18**) and Cl-platencin (**19**).

unit **6** under these conditions resulted in a sharp drop of yield (17% of **18**), whereas coupling with F-western unit **7** failed altogether. Thus, for the coupling of **4** with **6** we explored other conditions and found that HATU gave a slightly better result (27% yield of **19**). Even under these conditions **4** and **7** just gave traces of the desired product.

The biological data are summarized in Table 1. The modifications on the aromatic system (Cl-platencin and Cl-*iso*-platencin) resulted in a complete loss of antibacterial activity. This is in agreement with the simple guideline developed for the platensimycin pharmacophore.[7c] On the other hand the modification on the eastern part (*iso*-platencin) led to a highly potent and selective derivate. In fact it is the first derivate described so far that shows activity on a par with the parent natural products platencin and platensimycin. Its in vitro activity against various resistant *staphylococci* matches those of platencin. Interestingly it is also highly selective for *staphylococci* since it is ineffective against *Enterococci*.

Conclusion

In summary the synthesis of three new platencin analogs is reported. *iso*-Platencin (**17**) is the first derivate to show comparable activity to the parent natural product. Remarkably the core, *iso*-platensic acid **3**, was synthesized from perillaldehyde in only six steps. Therefore analogue **17** can be obtained quickly and in good yield to serve as a lead structure in further biological investigations. Modification of the aromatic section delivered inactive compounds only. As an additional benefit, our route to the key precursor platensic acid **4** was optimized.

Experimental Section

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. Anhydrous CH_2Cl_2 was distilled from CaH_2 under argon. Anhydrous THF (tetrahydrofuran) and DMF (*N*,*N*-dimethylformamide) was purchased from Acros. All other solvents were HPLC grade. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with E. Merck silica gel 60-F254 plates. Flash column chromatography was performed with Merck silica gel (0.04–0.063 mm, 240–400 mesh) under pressure. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on either Bruker Avance DRX 400 or DRX 600 MHz spectrometer. All NMR spectra were measured in $CDCl_3$ or MeOD solutions and referenced to the residual $CHCl_3$ signal (^{1}H, δ = 7.26 ppm; ^{13}C, δ = 77.00 ppm) or MeOH signal (^{1}H, δ = 3.31 ppm; ^{13}C, δ = 49.00 ppm). All ^{1}H and ^{13}C shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; b = broad signal). Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy. Optical rotations were measured on a P 341 Perkin–Elmer polarimeter. Mass spectra were measured on a Micro mass, trio 200 Fisions Instruments. High resolution mass spectra (HRMS) were performed with a Finnigan MAT 8230 with a resolution of 10000.

Methyl 5-chloro-2,4-dihydroxy-3-nitrobenzoate (20): A suspension of methyl 5-chloro-2,4-dihydroxybenzoate[9] (1.20 g, 5.92 mmol) in $CHCl_3$ (10 mL) was homogenized by the use of a ultrasonic bath (1 min) and treated with 65% HNO_3 (0.62 mL) at RT. After stirring for 100 min, water (20 mL) was added and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic phases were dried over magnesium sulfate, filtered and the solvent was removed under vacuum to yield phenol **20** (1.33 g, 90%) as a yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1H), 4.00 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1 (C), 158.2 (C), 156.3 (C), 136.0 (CH), 126.1 (C), 113.4 (C), 105.7 (C), 53.2 ppm (CH_3); IR: $\tilde{\nu}$ = 3500 (br), 1674, 1539, 1440, 1349, 1177 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_8H_6ClNO_6^+$: 246.9884, found: 246.9880 $[M]^+$.

Methyl 2,4-bis(benzyloxy)-5-chloro-3-nitrobenzoate (13): To a solution of phenol **20** (1.33 g, 5.37 mmol) in DMF (21 mL) was added K_2CO_3 (3.71 g, 26.9 mmol) and the suspension stirred for 15 min. After the addition of benzyl bromide (1.47 mL, 12.4 mmol) the mixture was heated to 60 °C for 20 h. Additional benzyl bromide (1.47 mL, 12.4 mmol) was added and stirring at 60 °C continued for 7 h. The suspension was filtered, diluted with water (100 mL) and the aqueous layer was extracted three times with ethyl acetate. The combined organic phases were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed under vacuum. Purification by column chromatography (40 g silica gel) using hexane/ethyl acetate 10:1 yielded **13** (1.12 g, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1H), 7.47–7.32 (m, 10H), 5.21 (s, 2H), 5.12 (s, 2H), 3.91 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3 (C), 150.5 (C), 150.2 (C), 135.4 (C), 134.9 (C), 134.3 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH, 2C), 128.6 (CH, 2C), 128.6 (CH, 2C), 128.6 (CH, 2C), 124.1 (C), 122.4 (C), 79.2 (CH_2), 77.2 (CH_2), 52.8 ppm (CH_3); IR: $\tilde{\nu}$ = 1733, 1545, 1372, 1292, 1252, 1147 cm^{-1}.

2,4-Bis(benzyloxy)-5-chloro-3-nitrobenzoic acid (21): To a solution of ester **13** (600 mg, 1.40 mmol) in THF (5.6 mL) was added water (1.4 mL)

Table 1. MIC (minimum inhibitory concentration [$\mu g\,mL^{-1}$]) values for platencin, *iso*-platencin, Cl-platencin and Cl-*iso*-platencin (Fus = fusidic acid; Pen G = Penicillin G; Van = Vancomycin;Doxy = doxycyclin; Linco = lincomycin; Cipro = ciprobay; Clarithro = clarithromycin R = resistant; S = sensitive).

BC-Code	Resistances	Platencin	Iso-platecin	Cl-platencin	Cl-iso-Platencin
Staphylococcus aureus (MSSA)	Fus^R (fusB)	0.8	0.4	>25.6	>25.6
Staphylococcus aureus (MSSA)	$PenG^R$ Amp^R	6.4	25.6	>25.6	>25.6
Staphylococcus aureus (MSSA)		1.6	0.8	>25.6	>25.6
Staphylococcus aureus (MSSA)	$Tiamulin^R$	1.6	1.6	>25.6	>25.6
Staphylococcus aureus (MSSA)	$Tiamulin^R$ $Linezolid^R$	0.4	0.4	>25.6	>25.6
Staphylococcus aureus (MSSA)	Fus^R (fusA)	0.4	1.6	>25.6	>25.6
Staphylococcus aureus (MRSA)	$Makrolid^R$ $Linco^R$ $Telithro^R$ $Cipro^R$	1.6	1.6	>25.6	>25.6
Staphylococcus haemolyticus	$Mupirocin^R$	0.4	0.4	>25.6	>25.6
Staphylococcus aureus (MRSA)	$Makrolid^R$ $Linco^R$ $Telithro^R$ $Cipro^S$	1.6	25.6	>25.6	>25.6
Staphylococcus aureus (MRSA)	Fus^R (not fusB) $Macrolid^R$ $Linco^S$ $Telithro^S$ $Cipro^S$	1.6	1.6	>25.6	>25.6
Staphylococcus aureus (MRSA)	$Makrolid^S$ $Linco^S$ $Telithro^S$ $Cipro^S$	1.6	12.8	>25.6	>25.6
Staphylocccus epidermidis (MRSE)	$Mupirocin^S$ Oxa^R Van^S	0.4	0.2	>25.6	>25.6
Staphylococcus epidermidis	$Mupirocin^R$ Oxa^S Van^S	0.1	0.1	>25.6	>25.6
Staphylococcus epidermidis	Fus^R (not fusB) $Mupirocin^S$ Van^R	0.2	0.8	>25.6	>25.6
Staphylococcus haemolyticus	$Cipro^R$ Ery^R $PenG^R$	0.2	0.4	>25.6	>25.6
Enterococcus faecalis	Amp^S Van^S $Makrolid^S$	0.2	>25.6	>25.6	>25.6
Enterococcus faecalis	Van^S $Doxy^S$ $Makrolid^R$	0.2	>25.6	>25.6	>25.6
Enterococcus faecalis (VRE)	Van^R $Doxy^R$ $Makrolid^R$	0.2	>25.6	>25.6	>25.6
Enterococcus faecalis (VRE)	Van^R $Doxy^R$ $Makrolid^R$	0.2	>25.6	>25.6	>25.6
Enterococcus faecium (VRE)	Van^R $Doxy^R$ $Makrolid^R$	>25.6	>25.6	>25.6	>25.6
Enterococcus faecium (VRE)	Van^R $Doxy^R$ $Makrolid^R$	>25.6	>25.6	>25.6	>25.6
Enterococcus faecium	Van^S $Doxy^R$ $Makrolid^R$	>25.6	>25.6	>25.6	>25.6
Enterococcus faecium	Amp^S Van^S $Makrolid^S$ $Cipro^R$	>25.6	>25.6	>25.6	>25.6
Moraxella catarrhalis	BRO-1 β-lactamase	0.2	>25.6	>25.6	>25.6
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Escherichia coli		>25.6	>25.6	>25.6	>25.6
Streptococcus pneumoniae	no resistance	>2.56	>2.56	>2.56	>2.56
Streptococcus pneumoniae		>2.56	>2.56	>2.56	>2.56
Streptococcus pneumoniae		>2.56	>2.56	>2.56	>2.56
Streptococcus pneumoniae	$Makrolid^R$	>2.56	>2.56	>2.56	>2.56
Streptococcus pneumoniae (MDR)	$PenG^R$ $Clarithro^R$	>2.56	>2.56	>2.56	>2.56
Streptococcus pneumoniae (MDR)	$PenG^R$	>2.56	>2.56	>2.56	>2.56
Streptococcus pneumoniae (MDR)	$Makrolid^R$ Van^I $Doxy^I$	>2.56	>2.56	>2.56	>2.56

and $LiOH{\cdot}H_2O$ (2.94 g, 70.1 mmol) and the suspension was stirred for 20 h at 45 °C. After acidification with 3 N HCl and saturation of the solution with NaCl, the aqueous layer was extracted three times with $CHCl_3$. The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed under vacuum. Purification by column chromatography (50 g silica gel) using ethyl acetate yielded **21** (490 mg, 84 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s, 1H), 7.47–7.34 (m, 10H), 5.25 (s, 2H), 5.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3 (C), 151.5 (C), 150.4 (C), 135.1 (CH), 134.7 (C), 134.6 (C), 129.1 (CH), 129.1 (CH), 128.9 (CH, 2C), 128.8 (CH, 2C), 128.7 (CH, 2C), 128.7 (CH, 2C), 124.7 (C), 120.8 (C), 79.8 (CH_2), 77.3 ppm (CH_2); IR: $\tilde{\nu}$ = 1699, 1545, 1373, 1292, 696 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{21}H_{15}ClNO_6^-$: 412.0588, found: 412.0592 $[M-H]^-$.

3-Amino-5-chloro-2,4-dihydroxybenzoic acid (6): To a solution of acid **21** (490 mg, 1.18 mmol) in methanol (12 mL) was added 5 % Pd/C (84 mg) and the suspension was stirred for 26 h under an atmosphere of hydrogen. After filtration, the solvent was removed under vacuum to give a brownish solid. The crude material was taken up in boiling *i*PrOH (100 mL), filtered and the solvent again removed under vacuum to yield pure **6** (135 mg, 56 %). ^{1}H NMR (400 MHz, MeOD): δ = 7.31 ppm (s, 1H); ^{13}C NMR (100 MHz, MeOD): δ = 173.2 (C), 151.5 (C), 147.2 (C), 124.0 (C), 121.1 (CH), 112.8 (C), 107.4 ppm (C); IR: $\tilde{\nu}$ = 3000 (br), 1628, 1448, 1375, 1301 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_7H_5ClNO_4^-$: 201.9907, found: 201.9914 $[M-H]^-$.

Methyl 5-fluoro-2-hydroxy-4-methoxybenzoate (15): To crude 4-fluorobenzene-1,3-diol (4.65 g; prepared from 4.9 g resorcinol according to literature)[11] was added water (47 mL) and $KHCO_3$ (20.0 g) and the suspension heated to reflux. A constant stream of CO_2 was bubbled through the refluxing reaction mixture for 10 h. After the addition of water (100 mL), the aqueous phase was extracted four times with diethyl ether. The aqueous phase was acidified with HCl and extracted three times with diethyl ether. The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed under vacuum to give crude 5-fluoro-2,4-dihydroxybenzoic acid (4.0 g). To a solution of the crude material in DMF (42 mL) was added $KHCO_3$ (2.56 g, 25.5 mmol) and after 5 min. methyl iodide (1.4 mL, 23.2 mmol). After stirring at RT for 20 h, water (160 mL) was added and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with brine and dried over magnesium sulfate, silica gel was added and the solvent was carefully removed under vacuum. Purification of the adsorbed material by column chromatography (70 g silica gel) using hexane/ethyl acetate 7:1 → 3:1 yielded ester **15** (624 mg, 7 % over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 11.6 Hz, 1H), 6.51 (d, *J* = 7.1 Hz, 1H), 3.92 (s, 3H), 3.90 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9 (C), 159.7 (C), 154.1 (d, *J* = 12.6 Hz, C), 145.4 (d, *J* = 239.3 Hz, C), 115.2 (d, *J* = 20.7 Hz, CH), 103.4 (C), 101.2 (CH), 56.2 (CH_3), 52.2 ppm (CH_3); IR: $\tilde{\nu}$ = 1659, 1444, 1362, 1273, 1196, 955, 909, 787, 749 cm^{-1} ; HRMS (EI): *m*/*z*: calcd for $C_9H_9FO_4^+$: 200.0485, found: 200.0483 $[M]^+$.

Methyl 5-fluoro-2,4-dihydroxybenzoate (22): To a cooled (0 °C) suspension of $AlCl_3$ (2.50 g, 18.7 mmol) in CH_2Cl_2 (12.5 mL) was added ester **15** (624 mg, 3.12 mmol) dissolved in CH_2Cl_2 (24 mL). The mixture was stirred for 23 h at RT and quenched by the addition of water (100 mL) at 0 °C. The aqueous phase was extracted two times with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under vacuum. Purification by column chromatography (20 g silica gel) using hexane/ethyl acetate 4:1 yielded bisphenol **22** (531 mg, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 10.9 Hz, 1H), 6.57 (d, *J* = 7.3 Hz, 1H), 3.92 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (C), 159.7 (C), 150.3 (d, *J* =

16.2 Hz, C), 144.3 (d, J=231.0 Hz, C), 115.3 (d, J=20.5 Hz, CH), 105.0 (CH), 104.3 (d, J=6.6 Hz, C), 52.3 ppm (CH_3); IR: $\tilde{\nu}$ = 3562, 1663, 1632, 1437, 1363, 1286, 1250, 786 cm^{-1}; HRMS (EI): m/z: calcd for $C_8H_7FO_4^+$: 186.0328, found: 186.0326 $[M]^+$.

Methyl 5-fluoro-2,4-dihydroxy-3-nitrobenzoate (23): A suspension of phenol **22** (500 mg, 2.69 mmol) in $CHCl_3$ (4.5 mL) was homogenized by the use of a ultrasonic bath (1 min) and treated with 65% HNO_3 (0.28 mL) at RT. After stirring for 100 min. water (10 mL) was added and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic phases were dried over magnesium sulfate, filtered and the solvent was removed under vacuum to yield compound **23** (440 mg, 71%) as a yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.85 (d, J= 10.4 Hz, 1H), 4.00 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.3 (C), 156.0 (C), 150.3 (d, J=15.3 Hz, C), 143.7 (d, J=242.6 Hz, C), 126.2 (C), 121.8 (d, J=19.9 Hz, CH), 103.4 (d, J=6.1 Hz, C), 53.2 ppm (CH_3); IR: $\tilde{\nu}$ = 3000 (br), 1669, 1541, 1447, 1364, 1290, 1252, 1173 cm^{-1}; HRMS (EI): m/z: calcd for $C_8H_6FNO_6^+$: 231.0179, found: 231.0174 $[M]^+$.

Methyl 2,4-bis(benzyloxy)-5-fluoro-3-nitrobenzoate (16): To a solution of compound **23** (440 mg, 1.90 mmol) in DMF (9.4 mL) was added 60% NaH (182 mg, 4.56 mmol) at 0°C and the suspension stirred for 10 min. After the addition of benzyl bromide (0.60 mL, 5.02 mmol) the mixture was stirred at RT for 50 h. After the addition of brine (5 mL) and water (50 mL), the aqueous layer was extracted four times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and the solvent was removed under vacuum. Purification by column chromatography (20 g silica gel) using hexane/ethyl acetate 10:1 yielded ester **16** (420 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.80 (d, J= 12.6 Hz, 1H), 7.43–7.33 (m, 10H), 5.13 (d, J=1.9 Hz, 2H), 5.07 (s, 2H), 3.88 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=163.3 (C), 149.9 (d, J=248.1 Hz, C), 147.7 (d, J=2.9 Hz, C), 142.3 (d, J=14.6 Hz, C), 135.6 (C), 134.8 (C), 129.0 (C), 128.7 (C, 2C), 128.6 (C), 128.5 (C, 4C), 128.4 (C, 2C), 120.8 (d, J=22.7 Hz, CH), 119.9 (d, J=6.6 Hz, C), 79.1 (CH_2), 77.2 (CH_2), 52.7 ppm (CH_3); IR: $\tilde{\nu}$ = 1733, 1544, 1498, 1440, 1377, 1325, 1262, 1198, 735 cm^{-1}.

2,4-Bis(benzyloxy)-5-fluoro-3-nitrobenzoic acid (24): To a solution of ester **16** (380 mg, 0.92 mmol) in THF (3.7 mL) was added water (0.9 mL) and LiOH.H2O (1.93 g, 46.0 mmol) and the suspension was stirred for 20 h at 45°C. After acidification with 3N HCl and saturation of the solution with NaCl, the aqueous layer was extracted three times with $CHCl_3$. The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed under vacuum to yield **24** (350 mg, 96%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.91 (d, J=12.3 Hz, 1H), 7.42–7.34 (m, 10H), 5.40 (d, J= 2.0 Hz, 2H), 5.11 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.4 (C), 150.0 (d, J=249.6 Hz, C), 147.8 (d, J=2.9 Hz, C), 143.3 (d, J= 14.6 Hz, C), 141.8 (C), 134.6 (C), 129.1 (C), 129.1 (C), 128.9 (C, 2C), 128.7 (C, 4C), 128.4 (C, 2C), 121.5 (d, J=22.7 Hz, CH), 118.3 (d, J= 6.6 Hz, C), 79.7 (CH_2), 76.6 ppm (CH_2); IR: $\tilde{\nu}$ = 1701, 1546, 1499, 1375, 1204, 696 cm^{-1}; HRMS (EI): m/z: calcd for $C_{21}H_{15}FNO_6^-$: 396.0883, found: 396.0873 $[M-H]^-$.

3-Amino-5-fluoro-2,4-dihydroxybenzoic acid (7): To a solution of acid **24** (350 mg, 0.88 mmol) in methanol (9 mL) was added 5% Pd/C (63 mg) and the suspension was stirred for 25 h under an atmosphere of hydrogen. After filtration, the solvent was removed under vacuum to give crude acid **7** (160 mg, 97%) which was used without further purification. ^{1}H NMR (400 MHz, MeOD): δ=7.01 ppm (d, J=11.1 Hz, 1H); ^{13}C NMR (100 MHz, MeOD): δ=173.6 (C), 149.2 (C), 146.5 (d, J= 229.1 Hz, C), 139.7 (d, J=19.0 Hz, C), 124.7 (C), 105.9 (d, J=21.2 Hz, CH), 104.8 ppm (d, J=8.1 Hz, C); IR: $\tilde{\nu}$ = 3073 (br), 1577, 1511, 1466, 1307, 889, 740 cm^{-1}; HRMS (EI): m/z: calcd for $C_7H_5FNO_4^-$: 186.0203, found: 186.0200 $[M-H]^-$.

(5*S*,6*S*,8*S*)-5,9-Dimethyltricyclo[6.2.2.0^{1,6}]dodeca-2,9-dien-4-one (9): To a solution of enone **8** (380 mg, 2.02 mmol) in THF (25 mL) was added 0.5 M KHMDS in toluene (6.1 mL, 3.03 mmol) slowly at −78°C. After 30 min., HMPA (5 mL) and MeI (1.00 mL, 16.1 mmol) was added sequentially. After 4 h, the reaction was quenched by the addition of sat. aq. $NaHCO_3$ solution and extracted with EtOAc (×3). The combined organic phase was washed with water, brine, dried over magnesium sulfate and concentrated under vacuum. Purification by column chromatography (30 g silica gel) using hexane/ethyl acetate 10:1 yielded compound **9** (325 mg, 80%). $[\alpha]_D^{20}$ = −148.5 (c=1.55, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.90 (d, J=10.1 Hz, 1H), 5.93 (d, J=10.1 Hz, 1H), 5.77 (s, 1H), 2.42–2.38 (m, 1H), 2.31–2.22 (m, 1H), 1.81 (d, J=1.7 Hz, 3H), 1.79–1.70 (m, 2H), 1.65–1.53 (m, 2H), 1.41–1.23 (m, 2H), 1.17–1.10 (m, 1H), 1.13 ppm (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.4 (C), 155.9 (CH), 142.4 (C), 128.9 (CH), 128.0 (CH), 45.7 (CH), 44.0 (CH), 39.6 (C), 35.9 (CH), 31.4 (CH_2), 27.4 (CH_2), 26.0 (CH_2), 20.1 (CH_3), 12.8 ppm (CH_3); IR: 2935, 1676, 1445, 823 cm^{-1}; HRMS (EI): m/z: calcd for $C_{14}H_{18}O$: 202.1358, found: 202.1357 $[M]^+$.

Methyl 3-[(5*S*,6*R*,8*S*)-5,9-dimethyl-4-oxotricyclo[6.2.2.0^{1,6}]dodeca-2,9-dien-5- yl]propanoate (10): To a solution of **9** (200 mg, 0.99 mmol) in diethyl ether (2.9 mL) and *tert*-butanol (2.9 mL) was added potassium *tert*-butoxide (222 mg, 1.98 mmol) at 0°C. After stirring at this temperature for 5 min methyl acrylic ester (0.71 mL, 7.91 mmol) was added. After 40 min the reaction was quenched by the addition of saturated aq. NH_4Cl and the aqueous layer was extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and the solvent was removed under vacuum. Purification by column chromatography (20 g silica gel) using hexane/ethyl acetate 10:1 yielded a crude diastereomeric mixture of esters (220 mg, d.r. 10:1) as colorless oil. Purification by HPLC yielded ester **10** (180 mg, 63%) as an analytically pure material. $[\alpha]_D^{20}$ = −84.7 (c=1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.82 (d, J=10.1 Hz, 1H), 5.91 (d, J=10.1 Hz, 1H), 5.81 (s, 1H), 3.63 (s, 3H), 2.50–2.44 (m, 1H), 2.22–2.08 (m, 3H), 1.97–1.84 (m, 2H), 1.80 (d, J=1.7 Hz, 3H), 1.61–1.39 (m, 4H), 1.35–1.20 (m, 2H), 1.17 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.2 (C), 174.0 (C), 154.7 (CH), 141.1 (C), 131.1 (CH), 127.2 (CH), 51.5 (CH_3), 47.2 (C), 42.4 (CH), 39.6 (C), 35.8 (CH), 31.6 (CH_2), 29.5 (CH_2), 27.6 (CH_2), 26.0 (CH_2), 25.5 (CH_2), 20.4 (CH_3), 20.2 ppm (CH_3); IR: $\tilde{\nu}$ = 2931, 1739, 1674, 1436, 1174, 829 cm^{-1}; HRMS (EI): m/z: calcd for $C_{18}H_{24}O_3$+Na^+: 311.1623, found: 311.1620 $[M+Na]^+$.

Methyl 3-[(5*S*,6*R*,8*S*)-5,9-dimethyl-4-oxotricyclo[6.2.2.0^{1,6}]dodeca-2,9-dien-5-yl]propanoic acid (3): To a solution of ester **10** (85 mg, 0.294 mmol) in THF (3.5 mL) was added 1 M aq. NaOH (3.5 mL) and stirred for 23 h at RT. After the addition of water (30 mL) and brine (15 mL) the mixture was washed with diethyl ether twice. The aqueous phase was acidified with 1.2 M HCl (formation of a white precipitate) and extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and the solvent was removed under vacuum to give acid **3** (77 mg, 95%). $[\alpha]_D^{20}$ = −73.1 (c=0.55, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.83 (d, J=10.1 Hz, 1H), 5.92 (d, J=10.1 Hz, 1H), 5.81 (s, 1H), 2.51–2.45 (m, 1H), 2.23–2.14 (m, 3H), 1.97–1.84 (m, 2H), 1.80 (d, J=1.7 Hz, 3H), 1.61–1.39 (m, 4H), 1.34–1.20 (m, 2H), 1.17 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.3 (C), 178.7 (C), 154.8 (CH), 141.2 (C), 131.1 (CH), 127.2 (CH), 47.2 (C), 42.5 (CH), 39.6 (C), 35.8 (CH), 31.3 (CH_2), 29.2 (CH_2), 27.5 (CH_2), 26.0 (CH_2), 25.5 (CH_2), 20.4 (CH_3), 20.2 ppm (CH_3); IR: $\tilde{\nu}$ = 2930, 1709, 1674, 1295, 414 cm^{-1}; HRMS (EI): m/z: calcd for $C_{17}H_{22}O_3$+Na^+: 297.1467, found: 297.1465 $[M+Na]^+$.

Methyl-3-[(5*S*,6*R*,8*S*)-5-methyl-9-methylidene-4-oxotricyclo[6.2.2.0^{1,6}]dodec-2-en-5-yl]propanoate (25): To a solution of ester **10** (295 mg, 1.02 mmol) in CH_2Cl_2 (5 mL) was added TFA (1.35 mL) at 0°C and stirred for 15 min at this temperature. The cooling bath was removed and stirring continued for 2 h. Methanol (30 mL) and K_2CO_3 (3.6 g) were added and the mixture stirred until complete consumption of the starting material. The suspension was filtered, water was added and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic phases were dried over magnesium sulfate, filtered and the solvent was removed under vacuum. Purification by column chromatography (20 g silica gel) using hexane/ethyl acetate 2:1 → 1:1 yielded alcohol **11** (280 mg, 89%) as a inconsequential diastereomeric mixture, which was directly used for the next step.

To a solution of alcohol **11** (280 mg, 0.91 mmol) in CH_2Cl_2 (5.7 mL) was added a solution of Martin's sulfurane (775 mg, 1.15 mmol) in CH_2Cl_2 (1.8 mL) at 0°C. Stirring was continued for 1 h at 0°C. The reaction mixture was concentrated under vacuum and the residue purified by column

chromatography (30 g silica gel) using hexane/ethyl acetate 7:1, to yield ester **25** (214 mg, 82%), which analytical data matched those reported in our earlier publication.[4h]

***iso*-Platencin (17)**: To a solution of acid **3** (14 mg, 0.051 mmol) in DMF (0.75 mL) were added $HOBt{\cdot}H_2O$ (10 mg, 0.065 mmol), DMAP (1 mg, 0.0082 mmol) and EDC (12 mg, 0.063 mmol). After 4 h, amine **5** (17 mg, 0.101 mmol) was added and stirring continued for 40 h. Water (10 mL) was added and the pH adjusted to 4 by the addition of 1 M HCl. The aqueous layer was extracted four times with CH_2Cl_2. The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed under vacuum. Purification by column chromatography (5 g silica gel) using EtOAc/hexane/AcOH/MeOH/H_2O 60:40:0.5:1.0:0.5 yielded **17** (11 mg, 51%). $[\alpha]_D^{20} = -107.7$ ($c = 0.35$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.19$ (s, 1H), 7.62 (d, $J = 9.0$ Hz, 1H), 6.83 (d, $J = 10.1$ Hz, 1H), 6.51 (d, $J = 9.0$ Hz, 1H), 6.01 (d, $J = 10.1$ Hz, 1H), 5.83 (s, 1H), 2.55–2.49 (m, 1H), 2.43–2.31 (m, 2H), 2.23–2.15 (m, 1H), 2.00–1.91 (m, 2H), 1.84–1.76 (m, 1H), 1.81 (d, $J = 1.6$ Hz, 3H), 1.65–1.25 ppm (m, 5H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 206.2$ (C), 174.1 (C), 173.1 (C), 156.7 (CH), 155.5 (C), 154.4 (C), 141.5 (C), 130.7 (CH), 128.3 (CH), 126.9 (CH), 114.4 (C), 111.3 (CH), 103.4 (C), 47.7 (C), 42.4 (CH), 39.8 (C), 35.7 (CH), 32.8 (CH_2), 32.4 (CH_2), 27.5 (CH_2), 25.9 (CH_2), 25.4 (CH_2), 20.5 (CH_3), 20.2 ppm (CH_3); IR: $\tilde{\nu} = 2928$, 1654, 1534, 1375 cm^{-1}; HRMS (EI): m/z: calcd for $C_{24}H_{27}NO_6+Na^+$: 448.1736, found: 448.1729 $[M+Na]^+$.

Cl-Platencin (19): To a solution of acid **4** (10 mg, 0.036 mmol) in DMF (0.20 mL) were added NEt_3 (25 uL, 0.18 mmol) and HATU (27 mg, 0.072 mmol). After 1 h, amine **6** (29 mg, 0.144 mmol) was added and stirring continued for 54 h. Water (5 mL) was added and the pH adjusted to 4 by the addition of 1 M HCl. The aqueous layer was extracted five times with CH_2Cl_2. The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed under vacuum. Purification by column chromatography (4 g silica gel) using acetone/hexane/AcOH 2:1:0 → 70:30:0.5 yielded **19** (4.5 mg, 27%). $[\alpha]_D^{20} = -24.4$ ($c = 0.09$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.28$ (s, 1H), 7.74 (s, 1H), 6.59 (d, $J = 10.1$ Hz, 1H), 5.93 (d, $J = 10.1$ Hz, 1H), 4.87 (s, 1H), 4.69 (s, 1H), 2.51–1.25 (m, 14H), 1.23 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 206.2, 174.6, 171.6, 156.4, 152.8, 151.5, 148.2, 127.6, 125.9, 115.5, 107.8, 47.7, 44.4, 44.2, 39.5, 36.4, 35.8, 32.3, 31.0, 28.0, 26.6, 21.2 ppm; IR: $\tilde{\nu} =$ 2927, 1653, 1534, 1126, 889, 739 cm^{-1}; HRMS (EI): m/z: calcd for $C_{24}H_{26}ClNO_6^-$: 458.1370, found: 458.1378 $[M-H]^-$.

Cl-*iso*platencin (18): To a solution of acid **3** (20 mg, 0.072 mmol) in DMF (0.80 mL) were added $HOBt{\cdot}H_2O$ (14 mg, 0.086 mmol), DMAP (2.0 mg, 0.016 mmol) and EDC (16 mg, 0.086 mmol). After 7 h, amine **6** (30 mg, 0.144 mmol) was added and stirring continued for 72 h. Water (10 mL) was added and the pH adjusted to 4 by the addition of 1 M HCl. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed under vacuum. Purification by column chromatography (4 g silica gel) using acetone/hexane/AcOH 2:1:0 → 70:30:0.5 yielded **18** (5.5 mg, 17%). $[\alpha]_D^{20} = -70.8$ ($c = 0.185$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (s, 1H), 7.75 (s, 1H), 6.95 (d, $J = 10.1$ Hz, 1H), 6.00 (d, $J = 10.1$ Hz, 1H), 5.82 (s, 1H), 2.52 (s, 1H), 2.46–2.27 (m, 2H), 2.19–2.15 (m, 1H), 2.00–1.87 (m, 2H), 1.81 (s, 3H), 1.81–1.72 (m, 1H), 1.64–1.52 (m, 2H), 1.52–1.28 (m, 2H), 1.27–1.25 (m, 1H), 1.24 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 206.2$, 174.5, 172.0, 156.8, 152.7, 151.0, 141.5, 130.7, 127.6, 126.9, 115.4, 47.7, 42.5, 39.8, 35.7, 32.7, 32.4, 27.5, 25.9, 25.4, 20.4, 20.2 ppm; IR: $\tilde{\nu} = 2927$, 1653, 1534, 1376, 878, 740 cm^{-1}; HRMS (EI): m/z: calcd for $C_{24}H_{26}ClNO_6^-$: 458.1370, found: 458.1375 $[M-H]^-$.

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