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Pseudoanguillosporin A and B: Two New Isochromans Isolated from the Endophytic Fungus *Pseudoanguillospora* sp.[‡]

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Two new isochromans named pseudoanguillosporin A (**2a**) and B (**3**), together with the known cephalochromin (**1**), were isolated from *Pseudoanguillospora* sp. The C-2 absolute configuration of **2a** and **3** was deduced from its CD spectrum by the isochroman helicity rule, supported by TDDFT CD calculations. The absolute configuration of the *sec*-hydroxyl group of **3** was determined by the Mosher NMR method from the MPA esters of its methylated derivative. The axial chirality of **1** was assigned through exciton analysis of its CD spectrum and confirmed by ZINDO CD calculations. The metabolites showed broad antimicrobial activities.

Introduction

In connection with our ongoing search for biologically active metabolites from fungi,[1] we investigated the constituents of an endophytic fungus, *Pseudoanguillospora* sp, internal strain number 6577, isolated from the red algae *Polyides rotundus* and found on the shore of the Baltic See near Ahrenshoop. The crude culture extract of the fungus was found to have good antifungal activity against *Microbotryum violaceum* and antibacterial activity against *Bacillus megaterium*. Extensive column and preparative thin-layer chromatography of the ethyl acetate culture extract afforded two new isochromans, named pseudoanguillosporin A (**2a**) and B (**3**), together with the known cephalochromin (**1**).[2–4] Cephalochromin (**1**) was recently identified as the first selective FabI [bacterial enoyl–acyl carrier protein (ACP) reductase] inhibitor of *Staphylococcus aureus* and *Escherichia coli*.[2]

3-Alkylisochromans are quite rare as natural products; the known derivatives include (3*S*)-6-hydroxy-8-methoxy-3,5-dimethylisochroman,[5] the anticoccidial arohynapene,[6] the toxic 8-hydroxy-6-methoxy-3,7-dimethylisochroman,[7] and the antibacterial bruguierol C.[8] Moreover, the isolated 1-hydroxy-3-heptylisochroman derivative CJ-12,373 was reported to have topoisomerase II inhibitor activity.[9] The absolute configurations of these isochroman derivatives have not been determined or are only tentatively proposed on the basis of biogenetic origin.[5b]

Results and Discussion

The first compound was crystallized from dichloromethane by dropwise addition of hexane as a yellow, amorphous powder. It was active against *Phytophthora infestans*, *Microbotryum violaceum*, *Botrytis cinerea*, *Pyricularia oryzae*, *Septoria tritici* and *Chlorella fusca* (see Tables 1 and 2). In the ^{13}C NMR spectrum, 10 aromatic carbon atoms, 1 carbonyl group, and 3 aliphatic carbon atoms were identified. With the use of HMQC and HMBC spectra, fragment **A** shown in Figure 1 was constructed.

The EI-MS with a molecular ion of 518.3 indicated that compound **1** is a dimer of fragment **A**, and the natural product was identified as the well-known cephalochromin[2] (**1**, Figure 2), first described by Tertzakian et al.[3] The structure was confirmed by comparison with the published data of the ^1H NMR spectrum.[4]

The axial chirality of cephalochromin (**1**) was previously determined as (a*S*) from its positive exciton couplet around 280 nm by comparison of its CD with those of other natural bis(naphtha-γ-pyrones) of known configuration.[10] Our

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Table 1. Biological activity of pure metabolites **1**, **2a**, and **3** against microbial test organisms in an agar diffusion assay; results as mm of radius of zone of inhibition.[a]

Metabolites or Standards	Concentration [mg]	Test organism		
		Bacillus megaterium	*Microbotryum violaceum*	*Chlorella fusca*
1	0.05	0	0	5 gi
1	0.25	0	5	5
2a	0.05	7 gi	5 gi	7
2a	0.25	7 + 6 gi	9	13
3	0.05	0	0	0
3	0.25	6 gi	7 gi	0
Penicillin	0.05	18	0	0
Tetracycline	0.05	18	0	10 gi
Nystatin	0.05	0	20	0
Actidione	0.05	0	50	35

[a] gi = growth inhibition, that is, there was some growth within the zone of inhibition.

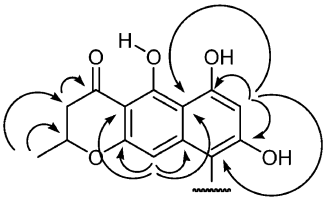
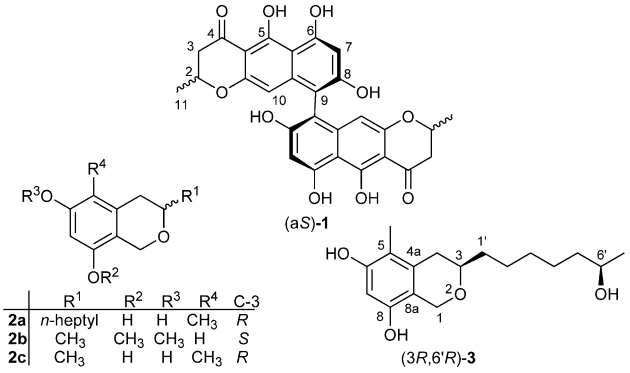


Figure 1. HMBC couplings of fragment **A** of compound **1**.



	R^1	R^2	R^3	R^4	C-3
2a	*n*-heptyl	H	H	CH_3	*R*
2b	CH_3	CH_3	CH_3	H	*S*
2c	CH_3	H	H	CH_3	*R*

Figure 2. Structures of cephalochromin (**1**), pseudoanguillosporins A and B (**2a**, **3**), synthetic isochroman derivative **2b**, and model **2c** used in the calculations.

cephalochromin sample also showed a positive CD couplet around 280 nm [292 (137.1), 264 (–129), Figure 3], suggesting the same (a*S*) axial chirality. This CD couplet is conceivably due to the exciton coupling[11] between the two electric-dipole allowed ^1B_b-like transitions, each of them having long-axis polarization in each aromatic unit.[10] In addition to the strong positive CD couplet, a weaker negative couplet above 300 nm and a positive one below 225 nm also appeared in the CD spectrum of **1**. Definitive and independent confirmation of the axial chirality of **1** came from comparison between experimental and calculated CD spectra. A conformational analysis was performed with the semiempirical PM3 method,[12] which offers accurate predictions of geometries and torsional energies of biaryl compounds.[13,14] Torsional PM3-energy scans around the C-9/C-9′ aryl linkage revealed the existence of an energy minimum for a $\omega_{C\text{-}8,C\text{-}9,C\text{-}9',C\text{-}8'}$ dihedral ≈ 90°. Subsequent DFT optimization [B3LYP/6-31G(d)] of that structure led to a slightly larger value ≈94°. The rest of the geometry (Figure 3, right) is dictated by a network of intramolecular hydrogen bonds and favorable OH–π interactions (see the conformation of 8- and 8′-OH). The pyrone ring assumes a half-chair conformation determined by the favored equatorial position of the C-2 methyl group. For the arbitrarily chosen (2*S*) configuration, the pyrone chirality is *M* (i.e., dihedral $\omega_{C\text{-}10a,O\text{-}1,C\text{-}2,C\text{-}3} < 0$).[15]

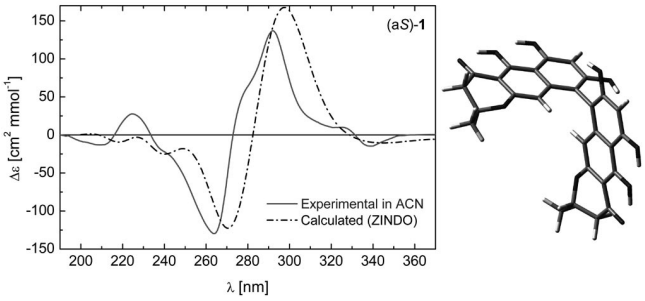


Figure 3. Measured (MeCN) and ZINDO-calculated CD spectra for cephalochromin [(a*S*)-**1**]. The calculation was run on the lowest-energy DFT structure for (a*S*)-**1** shown on the right.

In consideration of the large molecular size, a semiempirical NDO method was devised as the most proper to predict the CD spectrum of **1**, and ZINDO[16] was chosen for its good performance on systems with multiple aromatic chromophores.[14,17] A good agreement was obtained (Figure 3) between the experimental CD spectrum of **1** in acetonitrile and the ZINDO-calculated spectrum on the DFT-optimized structure with (a*S*) configuration, which confirms the axial chirality assumed above. Interestingly enough, MO analysis revealed that the couplet between 240–320 nm comes from the exciton coupling between three distinct transitions. In each naphtha-γ-pyrone chromophore, the first two (around 275 nm) are polarized along the C-4/C-9 direction, whereas the third (around 255 nm) is perpendicular to the first two.

The strong exciton coupled interaction between the two naphtha-γ-pyrones dominates the CD spectrum of their dimer **1**, even in the region of the n–π* transition, where each naphtha-γ-pyrone should show an intrinsic Cotton effect. In fact, the CD calculated for 2-methylnaphtha-γ-pyrone with the TDDFT method[18] [B3LYP/TZVP//B3LYP/6-31G(d)] is two orders of magnitude smaller than the exciton-coupled spectra shown in Figure 3. Therefore, the absolute configuration of the C-2 and C-2′ stereogenic centers could not be determined from the present CD data. A similar predominance of the axial chirality was previously observed in the phomoxanthone A CD spectrum[19] and seems to be of general importance in chiral biaryl systems. Currently, vibrational circular dichroism is being investigated to solve this problem, which has been waiting for a solution for more than 20 years.[10]

The second compound was obtained as a yellow optically active solid with a melting point of 46–48 °C. It was particularly active against *Pyricularia oryzae*, but also against *Phytophthora infestans*, *Botrytis cinerea*, *Septoria tritici*, *Bacillus megaterium* and *Chlorella fusca* (see Tables 1 and 2). The ^{1}H and ^{13}C NMR spectra revealed a pentasubstituted benzene ring, two methyl and eight CH_2 groups, as well as one CH unit. The HRMS spectrum gave a molecular ion at 278.18869, which is indicative of the molecular formula $C_{17}H_{26}O_3$. The chemical shift of the aromatic proton at δ = 6.21 ppm as well as that of the corresponding carbon atom at δ = 99.7 ppm suggested oxygenation at both *ortho* positions. Furthermore, the signal at δ = 1.98 ppm, and the two signals at δ = 2.33 and 2.57 ppm, can be assigned to a methyl and a methylene group attached to the benzene ring. The second CH_2 group gives rise to the two proton signals at δ = 4.51 and 4.85 ppm, suggesting both oxygenation and connection to the benzene ring. Both CH_2 groups are probably part of a ring system as the proton signals for each couple of C–H units are not isochronous. The chemical shift of 3.50 ppm for a CH group suggested further oxygenation, and the remaining six CH_2 groups together with the second methyl group form an aliphatic chain. Analysis of the 2D NMR spectra and the ^{1}H–^{1}H COSY spectrum led to isochroman structure **2a** (Figure 2) and this new natural product was named pseudoanguillosporin A after the fungus that produced the substance.

The absolute configuration of **2a** could be deduced from its CD spectrum (Figure 4). Pseudoanguillosporin A (**2a**) is a 3-substituted isochroman derivative, the characteristic ^1L_b band Cotton effects (CE) of which had been correlated with the *P*/*M*-helicity of the heteroring ($\omega_{C\text{-}8a,C\text{-}1,O\text{-}2,C\text{-}3} > \text{or} < 0$) and hence the absolute configuration of C-3.[20] It had been shown that *P*/*M*-helicity of the isochroman heteroring results in positive/negative ^1L_b band CE, regardless of the nature(s) and position(s) of substituents on the phenyl ring, even those having large spectroscopic moments (i.e., OMe, OH).[20] Because pseudoanguillosporin A (**2a**) shows a negative ^1L_b band CE [284 nm ($\Delta\varepsilon$ = –0.4 nm)], its heteroring adopts *M*-helicity (Figure 4, right), which implies a (3*R*) absolute configuration with an equatorial C-3 substituent. In contrast, (3*S*)-**2b**, a synthetic compound with known absolute configuration,[20] had positive ^1L_b band CE and *P*-helicity. Both (3*R*)-**2a** and (3*S*)-**2b** showed positive CE around 240 nm in the ^1L_a region, which is known to be more sensitive to the effect of achiral substituents of the aromatic ring.

The interpretation of the CD spectrum of compounds **2a** and **3** (vide infra) is supported by the calculation of the CD spectrum[21] of model compound (*R*)-**2c**. Its geometry was investigated with MMFF conformational searches and DFT [B3LYP/6-31G(d)] optimizations and revealed a strong prevalence (>98% at 300 K) of conformers with the C-3 substituent occupying the equatorial position. Four minima with populations >1% at 300 K (DFT energies) were found, differing only in the orientation of the two OH bonds; two of them, shown in Figure 5, contribute ca. 90% to the overall population. TDDFT calculations[22] using

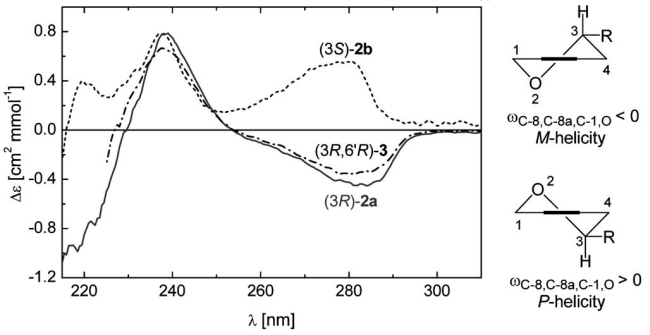


Figure 4. Left: measured CD spectra of (3*R*)-**2a**, (3*R*, 6′*R*)-**3**, and (3*S*)-**2b** in acetonitrile. Right: *P*- and *M*-helicity of the isochromane ring; pseudoanguillosporin A [(3*R*)-**2a**] and B [(3*R*,6′*R*)-**3**] have *M*-helicity.

various functionals (B3LYP, BH&HLYP, BP86) and TZVP basis set led to very similar CD spectra for the four structures. Moreover, their Boltzmann-weighted averages for (3*R*) absolute configuration reproduced well the pattern of bands discussed above for (*R*)-**2a**. The best match in terms of transition energies was obtained with the pure GGA functional BP86, as shown in Figure 5; hybrid functionals led to the same pattern of CD bands (–/+/– from the red), with some blueshift with respect to BP86 (20 nm for B3LYP, 50 nm for BH&HLYP). The first, long-wavelength negative CD band, experimentally observed for **2a** around 280 nm, is due to the ^1L_b transition, whereas the ^1L_a transition contributes to the second positive band observed around 240 nm. Both π–π* transitions, and especially the second one, are, however, superimposed to several valence-to-Rydberg transitions.

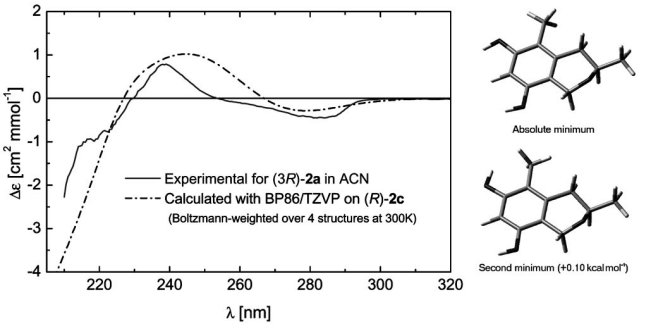
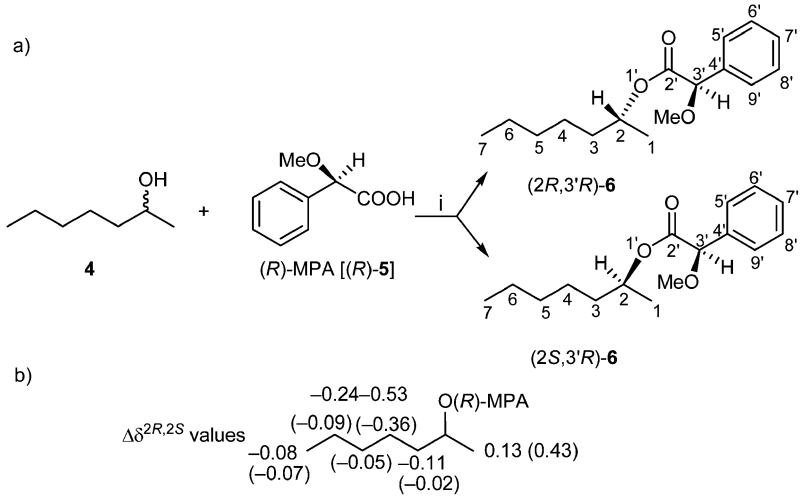


Figure 5. Experimental CD spectrum of pseudoanguillosporin A (**2a**) compared with the CD calculated on model compound (*R*)-**2c** with TDBP86/TZVP as Boltzmann average over four DFT-optimized structures [B3LYP/6-31G(d)]; the two most stable ones are shown on the right. The calculated spectrum has been scaled to 50% for better comparison.

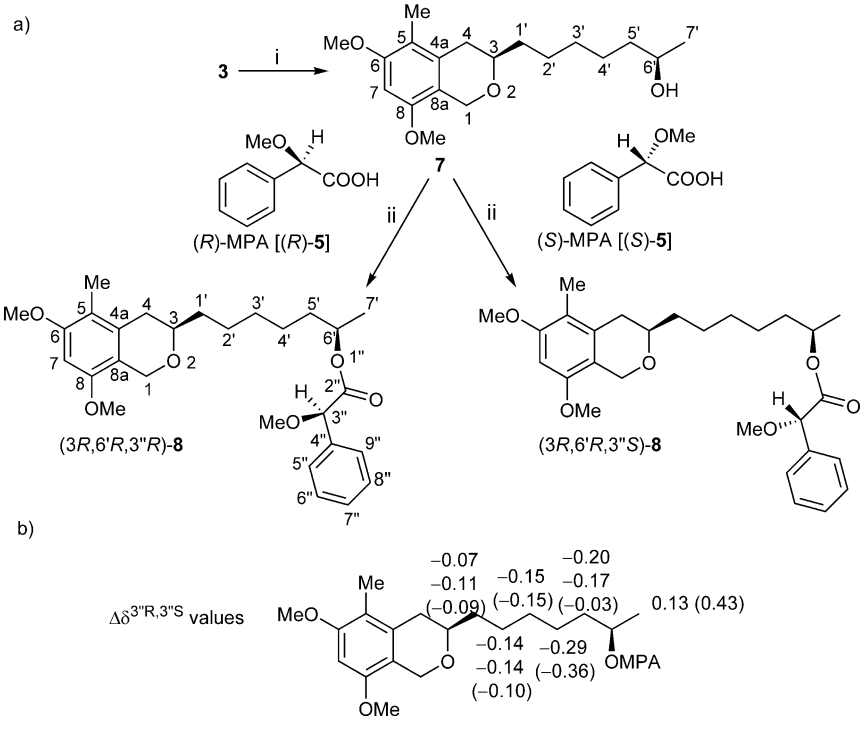
The third compound was obtained as a yellow optically active oil that moderately inhibited *Bacillus megaterium*, *Microbotryum violaceum*, *Botrytis cinerea* and *Phytophthora infestans* (see Tables 1 and 2). The NMR spectra had great similarity to those of pseudoanguillosporin A (**2a**, Figure 2). The main differences are seen in the chemical shift and coupling patterns of the terminal methyl group of the aliphatic chain and the CH group at δ = 3.73 ppm. The

HRMS spectrum suggested the molecular formula $C_{17}H_{26}O_4$. This result, in conjunction with the differences in the NMR spectra, suggested structure **3** (Figure 2) and the new metabolite was named pseudoanguillosporin B.

The absolute configuration of pseudoanguillosporin B (**3**) at C-3 was deduced as (*R*) from its CD spectrum. It was nearly identical to that of **2a**; the additional C-6′ stereogenic center, very distant from the chromophore, had practically no effect on the chiroptical properties (Figure 4). Not surprisingly, the optical rotations of pseudoanguillosporin A and B were also quite similar both in sign and magnitude (A: $[a]_D^{20} = -72.5$, B: $[a]_D^{20} = -72.8$). The absolute configuration of the C-6′ stereogenic center on the side chain of pseudoanguillosporin B was determined by Mosher's NMR method.[23] In order to check the reliability of the method, the (*R*)-MPA esters of readily available *rac*-2-heptanol (**4**) were prepared as model compounds by using (*R*)-MPA (**5**), and the resultant diastereomers were separated by preparative TLC (Scheme 1). In accordance with the conditions of Mosher's rule,[23] the consistent ^1H and ^{13}C chemical shift differences ($\Delta\delta^{2R,2S}$) allowed the configu-



Scheme 1. (a) i: EDC, DMAP, dry CH_2Cl_2, room temp. DMAP: 4-(*N*,*N*-dimethylamino)pyridine, EDC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, MPA: *a*-methoxyphenylacetic acid. (b) ^1H and ^{13}C (in brackets) chemical shift differences ($\Delta\delta^{2R,2S}$) of (2*R*,3′*R*)- and (2*S*,3′*R*)-**6**.



Scheme 2. (a) i: MeI, K_2CO_3, dry acetone, Δ. ii: EDC, DMAP, dry CH_2Cl_2. (b) ^1H and ^{13}C (in brackets) chemical shift differences ($\Delta\delta^{3''R,3''S}$) of (3*R*,6′*R*,3′′*R*)- and (3*R*,6′*R*,3′′*S*)-**8**.

ration of the diastereomers at C-2 to be assigned as (2*R*,3′*R*)- and (2*S*,3′*R*)-**6** (see Experimental Section for details).

Subsequently, the (*R*)-MPA ester of pseudoanguillosporin B [(3*R*,6′*R*,3′′*R*)-**8**] was prepared by the same procedure after protecting the phenolic hydroxy groups of **3** as its dimethyl ether **7** (Scheme 2). Comparison of its chemical shifts with those of (2*R*,3′*R*)- and (2*S*,3′*R*)-**6** (Scheme 1b), especially the similar H-7′ (H-1 in **6**) chemical shifts, suggested the (6′*R*) absolute configuration of pseudoanguillosporin B. This was unambiguously confirmed by the preparation of the diastereomeric (*S*)-MPA ester [(3*R*,6′*R*,3′′*S*)-**8**], whose NMR spectroscopic data were used to calculate the $\Delta\delta^{3''R,3''S}$ chemical shift differences by Mosher's protocol (Scheme 2).[23] The ^{1}H and ^{13}C differences showed consistent positive and negative values for the two sides flanking the stereogenic center in accordance with the previous (6′*R*) assignment.

Biological Activity

The antibacterial, fungicidal, and algicidal properties of the three compounds in comparison to four standard antibiotics were tested in an agar diffusion assay (Table 1), and for inhibitions of Oomycete and fungal test organisms in a microtiter assay in liquid media (Table 2). Although all three compounds were biologically active, the strongest inhibitions were caused by **2a**. Substances **2a** and **3** were antibacterial against the Gram-positive bacterium *Bacillus megaterium*. All three compounds were antifungal in both assays against the fungal and/or Oomycete test organisms. The best inhibitions of *P. infestans* were attained with compound **1** and **2a**. These substances were also antialgal against *Chlorella fusca*.

Table 2. Antifungal activities (values in %-growth in comparison to the controls).

Metabolite	*c* [ppm]	*Phytophthora infestans*	*Botrytis cinerea*	*Pyricularia oryzae*	*Septoria tritici*
1	125	2.6	50.3	5.8	10.9
	31	1.6	55.9	74.1	29.1
	8	6.3	75.2	87.4	61.5
	2	82.3	77.9	86.4	65.4
	0.5	100	81.5	85.4	72.8
	0.125	100	77.3	84.5	74
2a	125	5.3	0.2	0	3.9
	31	2.4	0.2	0.3	0.4
	8	58.5	42	0	0
	2	100	83.6	0	68.6
	0.5	100	82.3	87	100
	0.125	100	83.2	100	100
3	125	42.6	90.7	100	100
	31	85.1	85.6	92	100
	8	99.5	76	89.5	99.3
	2	95.2	79.8	88.9	90.4
	0.5	100	80.7	91.2	86.1
	0.125	99.9	81.4	89.7	85.3

Experimental Section

General Experimental Procedures: Melting points were determined in open capillaries with a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter. The IR spectra were taken with a NICOLET–510P spectrometer. NMR spectra were run with a Bruker ARX 200 or Bruker Avance 500 NMR spectrometer with TMS as internal standard. EI-MS were obtained with a MAT 8200 mass spectrometer. CD spectra were recorded with a J-810 spectropolarimeter by using 0.2, 1.0, 5.0, and 10.0 mm cells. Silica gel (230–400 mesh) was used for CC. Spots were detected on TLC under UV light or by heating after spraying with a reagent composed of 0.5 mL of anisaldehyde in 50 mL of HOAc/1 mL H_2SO_4.

Extraction and Isolation: The fungus *Pseudoanguillospora* sp. (6577) was isolated from the red alga *Polyides rotundus* from the shores of the Baltic Sea near Ahrenshoop and was cultivated for 21 d at room temperature on 5 L of biomalt solid agar. The agar plates were frozen for 3 d and filtered after thawing. Filtrate and mycelium were then separately extracted with ethyl acetate. After removal of the solvent under reduced pressure, 18 g of crude extract was obtained. The crude extract was then washed with hexane and dissolved in dichloromethane. The insoluble part was separated by filtration. Cephalochromin (**1**, 14.9 g) crystallized from the dichloromethane phase. The mother liquor was then separated by column chromatography with silica gel and a gradient of dichloromethane/methanol (0–10% methanol in 1% steps) in 5 fractions. From fraction 3, pseudoanguillosporin A (**2**) (1.5 g) was purified by preparative TLC on silica gel by using dichloromethane/methanol (93:7). Part of the extract was insoluble in dichloromethane; this part was dissolved in methanol and filtered. The methanol-soluble portion was then separated into 4 fractions by silica gel column chromatography by using the same gradient as before. Fraction 4 contained pseudoanguillosporin B (**3**, 222 mg), which was purified by preparative TLC on reverse-phase silica gel by using methanol/water (1:1).

Cephalochromin (1): Yellow, amorphous powder (CH_2Cl_2), m.p. >180 °C (decomp.) (ref.[4] >300 °C). $[\alpha]_D^{20}$ = +618 (*c* = 0.11, dioxane) {ref.[4] $[\alpha]_D^{20}$ = +727 (*c* = 0.19, dioxane)}. CD (MeCN, *c* = 2.84×10^{-4}): λ ($\Delta\varepsilon$) = 209 (–13.1), 224 (27.8), 238 sh. (–18.3), 264 (–129), 279 sh. (59.5), 292 (137.1), 326 (9.8), 338 (–14.6) nm. ^{1}H NMR (200 MHz, CD_3OD): δ = 1.44 (d, $J_{11,2}$ = 6.1 Hz, 6 H, 11-H, 11′-H), 2.70 (d, $J_{3,2}$ = 7.4 Hz, 4 H, 3-H, 3′-H), 4.51 (m, 2 H, 2-H, 2′-H), 5.94 (s, 2 H, 10-H, 10′-H), 6.17 (br. s, 2 H, 8-OH, 8′-OH), 6.53 (s, 2 H, 7-H, 7′-H), 9.63 (s, 2 H, 6-OH, 6′-OH), 14.98 (s, 2 H, 5-OH, 5′-OH) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 21.3 (C-11, C-11′, 2 C, CH_3), 43.6 (C-3, C-3′, 2 C, CH_2), 73.7 (C-2, C-2′, 2 C, CH), 100.0 (C-10, C-10′, 2 C, CH), 100.3 (C-7, C-7′, 2 C, CH), 102.7 (C-9, C-9′, 2 C, C_q)*, 102.8 (C-4a, C-4a′, 2 C, C_q)*, 105.8 (C-5a, C-5a′, 2 C, C_q), 142.6 (C-9a, C-9a′, 2 C, C_q), 156.7 (C-10a, C-10a′, 2 C, C_q), 160.5 (C-8, C-8′, 2 C, C_q), 161.1 (C-6, C-6′, 2 C, C_q), 164.8 (C-5, C-5′, 2 C, C_q), 198.9 (C-4, C-4′, 2 C, C_q) ppm. *Assignment of the signals is interchangeable. EI-MS (70 eV, 200 °C): *m*/*z* (%) = 518 (27.6) [M^+], 194 (8.8), 166 (9.5), 149 (14.3), 125 (10.6), 111 (13.3), 97 (21.3), 83 (27.3), 69 (36.3), 57 (64.4), 43 (100), 28 (95.6).

Pseudoanguillosporin A (2a): Yellow solid, m.p. 46–48 °C. $[\alpha]_D^{20}$ = –72.5 (*c* = 0.65, MeOH). CD (MeCN, *c* = 1.23×10^{-3}): λ ($\Delta\varepsilon$) = 198 (–9.8), 218 sh. (–1.0), 238 (0.7), 284 (–0.4) nm. UV (CH_3CN): λ (log ε) = 283 (3.42), 201 (4.72) nm. IR (film): $\tilde{\nu}$ = 3437, 3330, 2952, 2922, 2852, 1604, 1462, 1452, 1254, 1105, 1043 cm^{-1}. ^{1}H NMR (200 MHz, CD_3OD): δ = 0.92 (t, $J_{15,14}$ = 6.8 Hz, 3 H, 7′-H), 1.33 (m, 8 H, 3′-H, 4′-H, 5′-H, 6′-H), 1.42 (m, 1 H, 2′-H^a), 1.60 (m, 3 H, 1′-H, 2′-H^b), 1.98 (s, 3 H, 5-CH_3), 2.33 (dd, J_{gem} =

16.4 Hz, $J_{4a,3}$ = 10.8 Hz, 1 H, 4-H[a]), 2.57 (dd, J_{gem} = 16.4 Hz, $J_{4b,3}$ = 2.6 Hz, 1 H, 4-H[b]), 3.50 (m, 1 H, 3-H), 4.51 (d, J_{gem} = 14.7 Hz, 1 H, 1-H[a]), 4.85 (d, J_{gem} = 14.7 Hz, 1 H, 1-H[b]), 6.21 (s, 1 H, 7-H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 9.1 (5-CH_3), 13.2 (7′-CH_3), 22.4 (6′-CH), 25.4 (2′-CH_2), 29.1 (6′-CH_2)**, 29.5 (3′-CH_2)**, 31.7 (5′-CH_2), 32.3 (CH_2, C-4), 36.0 (1′-CH_2), 64.7 (CH_2, C-1), 75.0 (CH, C-3), 99.7 (CH, C-7), 112.7 (C_q, C-5)*, 112.8 (C_q, C-8a)*, 133.4 (C_q, C-4a), 150.8 (C_q, C-8), 153.5 (C_q, C-6) ppm. *Assignments marked with * and ** are interchangeable. EI-MS (70 eV, 200 °C): *m/z* (%) = 278 (20) [M$^+$], 179 (9), 150 (78), 99 (26), 86 (58), 57 (27), 44 (100), 28 (31). HRMS (EI): calcd. for $C_{17}H_{26}O_3$ 278.18819; found 278.18869.

Pseudoanguillosporin B (3): Yellow oil. $[\alpha]_D^{20}$ = –72.8 (*c* = 0.36, MeOH). UV (MeOH): λ (log ε) = 427 (4.64), 338 (5.39), 286 (6.36) nm. IR (Film): $\tilde{\nu}$ = 3383, 2931, 2858, 1606, 1462, 1335, 1259, 1107, 1045 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ = 1.17 (d, $J_{15,14}$ = 6.2 Hz, 3 H, 7′-H), 1.49 (m, 10 H, 1′-H, 2′-H, 3′-H, 4′-H, 5′-H), 1.98 (s, 3 H, 5-H), 2.33 (dd, J_{gem} = 16.6 Hz, $J_{4a,3}$ = 10.8 Hz, 1 H, 4-H[a]), 2.59 (dd, J_{gem} = 16.6 Hz, $J_{4b,3}$ = 2.2 Hz, 1 H, 4-H[b]), 3.51 (m, 1 H, 3-H), 3.73 (m, 1 H, 14-H), 4.50 (d, J_{gem} = 14.7 Hz, 1 H, 1-H[b]), 4.84 (d, J_{gem} = 14.7 Hz, 1 H, 1-H[a]), 6.21 (s, 1 H, 7-H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 9.0 (5-CH_3), 22.2 (CH_3, C-7′), 25.3 (CH_2, C-4′)**, 25.5 (CH_2, C-2′)**, 29.5 (CH_2, C-3′), 32.3 (CH_2, C-4), 35.8 (CH_2, C-1′), 38.8 (CH_2, C-5′), 64.6 (CH_2, C-1), 67.3 (CH, C-6′), 74.9 (CH, C-3), 99.6 (CH, C-7), 112.7 (C_q, C-5)*, 112.8 (C_q, C-8a)*, 133.4 (C_q, C-4a), 150.8 (C_q, C-8), 153.5 (C_q, C-6) ppm. * Assignments marked with * and ** are interchangeable. EI-MS (70 eV, 200 °C): *m/z* (%) = 294 (2) [M$^+$], 279 (3), 177 (5), 143 (13), 111 (7), 97 (11), 71 (18), 56 (32), 45 (62), 31 (100). HRMS (EI): calcd. for $C_{17}H_{26}O_4$ 294.18311; found 294.18316.

(*R*)-α-MPA Esters of (±)-Heptan-2-ol [(2*R*,3′*R*)- and (2*S*,3′*R*)-6]: A stirred solution of (*R*)-α-MPA [(*R*)-**5**] (175 mg, 1 mM), EDC (200 mg, 1 mM), and DMPA (20 mg, 0.16 mM) in anhydrous dichloromethane (4.5 mL) was treated dropwise with a solution of (±)-heptane-2-ol (0.05 mL, 0.35 mM) in anhydrous dichloromethane (2 mL) and stirring was continued for 24 h at room temperature. After washing the reaction mixture with a solution of $NaHCO_3$ and then with water, the organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The raw material was purified by preparative TLC on silica gel (hexane/EtOAc, 6:1) to give two products, (*R*)- and (*S*)-ester of the starting material as oils (38 and 32 mg, 41 and 34%, respectively). Data for (*R*)-α-MPA-ester of (2*R*)-heptan-2-ol: $[\alpha]_D^{20}$ = –48.9 (*c* = 1.27, chloroform). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.77 (t, 3 H, 7-H), 0.86 (m, 2 H, 6-H)*, 1.00 (m, 4 H, 4-H, 5-H)*, 1.21 (d, *J* = 6.5 Hz, 3 H, 1-H), 1.42 (m, 2 H, 3-H), 3.41 (s, 3 H, 3′-OMe), 4.71 (s, 1 H, 2′-H), 4.93 (m, 1 H, 2-H), 7.32–7.44 (m, 5 H, Ph) ppm. ^{13}C NMR (90 MHz, $CDCl_3$): δ = 13.85 (C-7), 20.02 (C-1), 22.37 (C-6), 24.56 (C-4), 31.33 (C-5), 35.67 (C-3), 57.21 (2′-OMe), 71.98 (C-2), 82.68 (C-3′), 127.1 (C-6′, C-7′, C-8′), 128.51 (C-5′, C-9′), 136.52 (C_q-4′), 170.36 (C_q-2′) ppm. *Assignment of the signals is interchangeable. Data for (*R*)-MPA-ester of (2*S*)-heptan-2-ol: $[\alpha]_D^{20}$ = –25.4 (*c* = 1.08, chloroform). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.85 (t, 3 H, 7-H), 1.08 (d, *J* = 6.1 Hz, 3 H, 1-H), 1.24–1.53 (m, 8 H, 4-H, 5-H, 6-H)*, 1.53 (m, 2 H, 3-H), 3.42 (s, 3 H, 3′-OMe), 4.74 (s, 1 H, 2′-H), 4.97 (m, 1 H, CH, 2-H), 7.31–7.46 (m, 5 H, Ph) ppm. ^{13}C NMR (90 MHz, $CDCl_3$): δ = 13.92 (C-7), 19.59 (C-1), 22.46 (C-6), 24.92 (C-4), 31.38 (C-5), 35.69 (C-3), 57.28 (2′-OCH_3), 72.06 (C-2), 82.79 (C-3′), 127.01 (C-6′, C-7′, C-8′), 128.49 (C-5′, C-9′), 136.27 (C_q-4′), 170.37 (C_q-2′) ppm, *Assignment of the signals is interchangeable.

6,8-Dimethyl Ether of Pseudoanguillosporin B (7): To a suspension of pseudoanguillosporin B (**3**) (23 mg, 0.08 mM) and K_2CO_3 (66 mg, 0.48 mM) in dry acetone (5 mL) was added MeI (50 mg, 0.34 mM). The reaction mixture was heated at reflux for 24 h and then filtered. The solvent was evaporated under reduced pressure, and the residue was diluted with water and extracted with EtOAc. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure, and the residue was purified by preparative TLC (hexane/EtOAc, 1:7) to yield a pale-yellow oil (16 mg, 64%) that crystallized during cooling to give a white, amorphous powder ($CHCl_3$). M.p. 32–37 °C. $[\alpha]_D^{20}$ = –86.2 (*c* = 0.115, chloroform). IR (film): $\tilde{\nu}$ = 3364, 2966, 2938, 2922, 2830, 2864, 2843, 1454, 1054, 1032, 1016 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (d, $J_{7',6'}$ = 6.5 Hz, 3 H, 7′-H), 1.31 (m, 2 H, 3′-H), 1.35 (m, 2 H, 2′-H), 1.42 (m, 2 H, 5′-H), 1.51 (m, 2 H, 4′-H), 1.55 (m, 2 H, 1′-H), 1.97 (s, 3 H, 5-H), 2.35 (dd, *J* = 16.5, 11 Hz, 4-H_{ax}), 2.53 (dd, *J* = 16.5, 2.0 Hz, 1 H, 4-H_{eq}), 3.42 (s, 1 H, OH), 3.47 (m, 1 H, 3-H), 3.73 (s, 3 H, 6-OMe), 3.75 (s, 3 H, 8-OMe), 3.76 (m, 1 H, 6′-H), 4.48 (d, *J* = 15 Hz, 1 H, 1-H$_a$), 4.82 (d, *J* = 15 Hz, 1 H, 1-H$_b$), 6.27 (s, 1 H, 7-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.12 (5-Me), 23.50 (C-7′), 25.58 (C-2′), 25.71 (C-4′), 29.67 (C-4), 32.42 (C-3′), 36.11 (C-1′), 39.30 (C-5′), 55.29 (6-OCH_3), 55.94 (8-OCH_3), 64.72 (C-1), 68.14 (C-6′), 74.45 (C-3), 92.83 (C-7), 115.81 (C_q-8), 121.77 (C_q-5a), 134.12 (C_q-8a), 156.46 (C_q-6), 161.12 (C_q-8) ppm. *Assignment of the signals is interchangeable. HRMS (EI): calcd. for $C_{19}H_{30}NaO_4$ 345.204; found 345.204.

(*R*)-α-MPA Ester of 6,8-Dimethyl Ether of Pseudoanguillosporin B [(3*R*,6′*R*,3′′*R*)-8]: A stirred solution of (*R*)-(–)-α-MPA [(*R*)-**5**] (13 mg, 0.08 mM), EDC (15 mg, 0.08 mM), and DMPA (3.8 mg, 0.03 mM) in anhydrous dichloromethane (2.5 mL) was treated dropwise with a solution of **7** (8.6 mg, 0.03 mM) in anhydrous dichloromethane (1 mL). Stirring was continued for 20 h at room temperature, and the reaction mixture was washed with $NaHCO_3$ solution and then with water. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc, 2:1) to give a white, amorphous powder (7.6 mg, 60%) ($CHCl_3$). M.p. 64–67 °C. $[\alpha]_D^{20}$ = –94.9 (*c* = 0.305, chloroform). IR (film): $\tilde{\nu}$ = 3033, 2992, 2968, 2933, 2859, 2835, 1737, 1596, 1492, 1452, 1378, 1319, 1214, 1125, 1095 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02 (m, 2 H, 4′-H), 1.16 (m, 2 H, 3′-H), 1.22 (d, $J_{7',6'}$ = 6.5 Hz, 3 H, 7′-H), 1.25 (m, 1 H, 2′-H$_a$), 1.36 (m, 1 H, 2′-H$_b$), 1.39 (m, 1 H, 5′-H$_a$), 1.47 (m, 2 H, 1′-H$_a$, 5′-H$_b$), 1.57 (m, 1 H, 1′-H$_b$), 2.05 (s, 3 H, 5-Me), 2.39 (dd, *J* = 16.5, 11 Hz, 1 H, 4-H_{ax}), 2.57 (dd, *J* = 16.5, 2.5 Hz, 1 H, 4-H_{eq}), 3.41 (s, 3 H, 3′′-OMe), 3.48 (m, 1 H, 3-H), 3.80 (s, 3 H, 6-OMe), 3.83 (s, 3 H, 8-OMe), 4.54 (d, *J* = 15.5 Hz, 1-H$_a$), 4.72 (s, 1 H, 3′′-H), 4.89 (d, *J* = 15.0 Hz, 1-H$_b$), 4.95 (m, 1 H, 6′-H), 6.34 (s, 1 H, 7-H), 7.31–7.45 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.12 (5-Me), 20.06 (C-7′), 25.38 (C-2′), 24.91 (C-4′), 29.29 (C-3′), 32.39 (C-4), 35.70 (C-5′), 36.00 (C-1′), 55.3 (6-OMe), 55.94 (8-OMe), 57.25 (3′′-OMe), 64.67 (C-1), 72.06 (C-6′), 74.39 (C-3), 82.72 (C-3′′), 92.87 (C-7), 115.82 (C_q-5)*, 115.99 (C_q-8a)*, 127.06 (C-7′′), 127.21 (C-5′′, C-9′′), 128.52 (C-6′′, C-8′′), 134.11 (C-4′′), 136.58 (C_q-5a), 153.87 (C_q-8), 156.49 (C_q-6), 170.37 (C_q-2′′) ppm. *Assignment of the signals is interchangeable. HRMS: calcd. for $C_{28}H_{38}NaO_6$ [M$^+$] 493.257; found 493.255.

(*S*)-α-MPA Ester of 6,8-Dimethyl Ether of Pseudoanguillosporin B [(3*R*,6′*R*,3′′*S*)-8]: A solution of **7** (7 mg, 0.02 mM) in anhydrous dichloromethane (1 mL) was added dropwise to a stirred solution of (*S*)-α-MPA [(*S*)-**5**] (12 mg, 0.07 mM), EDC (13 mg, 0.07 mM), and DMPA (1.3 mg, 0.01 mM) in dry dichloromethane (2.5 mL) and stirring was continued for 24 h at room temperature. After washing the reaction mixture with a solution of $NaHCO_3$ and then with water, the organic layer was dried with $MgSO_4$ and the solvents evaporated. The raw material was purified by preparative

TLC (hexane/EtOAc, 2:1) to give a colorless oily material (5 mg, 50%) ($CHCl_3$). $[\alpha]_D^{20} = -38.6$ ($c = 0.27$, chloroform). IR (film): $\tilde{\nu}$ = 3060, 3027, 2998 sh., 2969 sh., 2931, 1740, 1599, 1490, 1455, 1364, 1318, 1216, 1123, 1091 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.09 (d, $J_{7',6'}$ = 6 Hz, 3 H, 7′-H), 1.31 (m, 4 H, 3′-H, 4′-H), 1.39 (m, 1 H, 2′-H_a), 1.50 (m, 2 H, 2′-H_b, 5′-H_a), 1.58 (m, 1 H, 1′-H_a), 1.59 (m, 1 H, 5′-H_b), 1.64 (m, 1 H, 1′-H_b), 2.04 (s, 3 H, 5-Me), 2.41 (dd, J = 16.5, 10.5 Hz, 1 H, 4-H_{ax}), 2.59 (dd, J = 16.5, 2.5 Hz, 1 H, 4-H_{eq}), 3.42 (s, 3 H, 3′′-OMe), 3.52 (m, 1 H, 3-H), 3.80 (s, 3 H, 6-OMe), 3.82 (s, 3 H, 8-OMe), 4.54 (d, J = 15 Hz, 1 H, 1-H_a), 4.74 (s, 1 H, 3′′-H), 4.89 (d, J = 15 Hz, 1 H, 1-H_b), 4.97 (6′-H), 6.34 (s, 1 H, 7-H), 7.36 (m, 3 H, 6′′, 7′′, 8′′-H), 7.42 (m, 2 H, 5′′, 9′′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.12 (5-Me), 19.63 (C-7′), 25.27 (C-2′)*, 25.48 (C-4′)*, 29.45 (C-3′), 32.41 (C-4), 35.73 (C-5′), 36.09 (C-1′), 55.30 (6-OMe), 55.93 (8-OMe), 57.30 (3′′-OMe), 64.71 (C-1), 72.06 (C-6′), 74.41 (C-3), 82.77 (C-3′′), 92.85 (C-7), 115.81 (C_q-5)*, 115.99 (C_q-8a)*, 127.06 (C-4′′, C-9′′), 127.27 (C-7′′), 128.53 (C-6′′, C-8′′), 134.1 (C-4′′), 136.43 (C-5a), 153.86 (C_q-8), 156.48 (C_q-6), 170.38 (C_q-2′′) ppm. *Assignment of the signals is interchangeable. HRMS: calcd. for $C_{28}H_{38}NaO_6$ [M^+] 493.257; found 493.254.

Tests for Biological Activity: For the agar diffusion assay, the compounds were dissolved in a mixture of acetone and methanol (1:1) at a concentration of 1 and 5 $\mu g\,\mu L^{-1}$. Fifty microliters of the solution were pipetted onto a sterile filter disc (final concentrations of 0.05 and 0.25 mg/filter disc), which was placed onto an appropriate agar growth medium for the respective test organism (*Bacillus megaterium, Microbotryum violaceum*, and *Chlorella fusca*) and subsequently sprayed with a suspension of the test organism.[24]

For the microtiter assay in liquid media for antifungal activities, *Septoria tritici* and *Pyricularia oryzae* were cultivated in YBG [10 g yeast extract (Bacto from Difco), 10 g Bacto Peptone, 20 g glycerol (995), 1000 mL distilled water], *Botrytis cinerea* in YBA (as YBG, but with 20 g sodium acetate instead of glycerol), and the fungal-like *Phytophthora infestans* in D.D. Clarke medium (0.5 g KH_2PO_4, 0.25 g $MgSO_4/7H_2O$, 1.0 g asparagine, 5.0 g yeast extract, 2.0 g casamino acids, 25 g glucose, 0.001 g thiamine, 1000 mL distilled water). Stationary cultivation was at 18 °C for 7 d. The metabolites were tested at concentrations of 125, 31, 8, 2, 0.5, and 0.125 ppm.

Computational Section: Conformational searches (MMFF and PM3 methods) and geometry optimizations [DFT method, B3LYP/6-31G(d) level] were run with Spartan06, Wavefunction, Inc., Irvine CA, with default parameters and convergence criteria. CD calculations were run with Gaussian03W.[25] All calculated structures and spectra are available upon request to the authors. Rotational strengths were computed with the semiempirical ZINDO-S/CI method[16] including all possible configurational interactions (full CI), or with the TDDFT method by using various functionals (B3LYP,[26] BH&HLYP,[27] BP86[28]) and the TZVP basis set.[29] CD spectra were generated as the sum of Gaussians with 1500 and 2500 cm^{-1} half-height widths, respectively for **1** and **2c**, by using dipole–velocity computed rotational strengths. For **2c**, the first 4–6 states, depending on the functional, had transition energies below the estimated ionization potential (5.85 eV, B3LYP/TZVP).[30] They include the aromatic ^1L_b and ^1L_a transitions that contribute to the first two observed CD bands.

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