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Planar chiral analogues of PRODAN based on a [2.2]paracyclophane scaffold: synthesis and photophysical studies

Simon Felder,^a Marie-Léonie Delcourt,^a Manon H. E. Bousquet,^b Denis Jacquemin,^{*,b} Rafael Rodríguez,^c Ludovic Favereau,^c Jeanne Crassous,^{*c} Laurent Micouin^{*,a} and Erica Benedetti^{*,a}

(a) Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques - UMR8601 CNRS, Université de Paris, 45 rue des Saints Pères, 75006 Paris, France.

(b) Université de Nantes, CNRS, CEISAM ULR 6230, F-44000 Nantes Cedex 3, France.

(c) Univ Rennes, Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS, Campus de Beaulieu, 35042 Rennes Cedex, France.

ABSTRACT: We describe the synthesis and photophysical characterization of differently substituted planar chiral analogues of PRODAN based on a [2.2]paracyclophane scaffold. This experimental and theoretical study highlights that the (chir)optical properties of the new “*phane*” compounds, which incorporate an electron-withdrawing propionyl moiety and an electron-donating dimethylamino group at their *para* or *pseudo-para* positions, strongly depend on their substitution patterns. In particular, for this series of molecules, a more pronounced solvatochromism and clear chiroptical behaviors are observed when the two substituents are placed on the two rings of the pCp core in a non “co-planar” arrangement (*pseudo-para* derivative). This observation may help designing of new pCp-based luminophores with finely tuned photophysical properties.

INTRODUCTION

Since their discovery in 1949,¹ [2.2]paracyclophane (pCp) and its derivatives have attracted considerable attention within the scientific community due to both their unique three-dimensional framework² and intriguing electronic properties. These compounds are indeed characterized by a rather rigid, sandwich-like structure which displays two benzene rings stacked in a face-to-face geometry and covalently linked together by two ethylene bridges at their *para* positions. The close proximity of the two π -conjugated systems gives rise to through-bond and through-space interactions which strongly influence the UV-Vis absorption and fluorescence emission profiles of pCps.³ As a result, these compounds have been widely employed as building blocks in material sciences, notably for the development of organic light-emitting diodes (OLEDs),⁴ and nonlinear optical systems.⁵ In addition, depending on their substitution patterns, [2.2]paracyclophanes can display planar chirality due to the hindered rotation of their aryl moieties.⁶ In recent years, this property, combined to the unusual spectroscopic behavior of pCps, has been exploited to obtain a variety of optically active dyes showing strong electronic circular dichroism (ECD) and circularly polarized luminescence (CPL). While the great majority of the CPL active pCp-based chromophores developed so far present “branched” π -extended structures or complex three-dimensional shapes,^{7,8} only few compact planar chiral dyes have been described to date.⁹ It is therefore of great

interest to design new straightforward routes for the preparation of such compounds in order to widen the chemical space of pCps and *in fine* access original CPL emitting organic molecules.

In our ongoing work on [2.2]paracyclophanes,¹⁰ we recently became interested in exploring the possibility to synthesize planar chiral solvatochromic dyes. In particular, we focused our attention on the preparation of pCp-analogues of PRODAN, a well-known solvent-sensitive planar fluorescent probe extensively used to study lipid bilayers and cellular membranes.¹¹ PRODAN is a push-pull charge-transfer chromophore characterized by a naphthalene-based π -conjugated system functionalized with a dimethylamino group and a propionyl moiety at its C-2 and C-6 positions (Figure 1). Changes in solvent polarity strongly influence the emission properties of PRODAN due to important dipole moment variations which occur upon excitation under light irradiation.¹² We considered replacing the two-dimensional naphthalene unit of this dye with the three-dimensional framework of [2.2]paracyclophane in order to investigate the influence of through-space conjugation on the photophysical properties of the resulting chromophores, and possibly tune their behaviors simply by playing with the spatial orientation of the electron-donating and electron-withdrawing substituents on the pCp core.

In this article, we detail different synthetic approaches for preparing *pseudo-para* and *para* substituted pCp-based analogues of PRODAN both in their racemic and enantiopure forms (Figure 1).

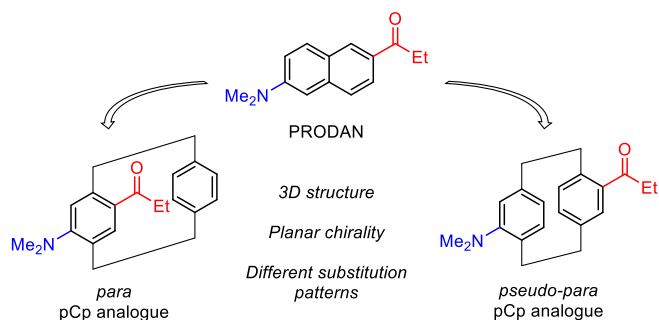


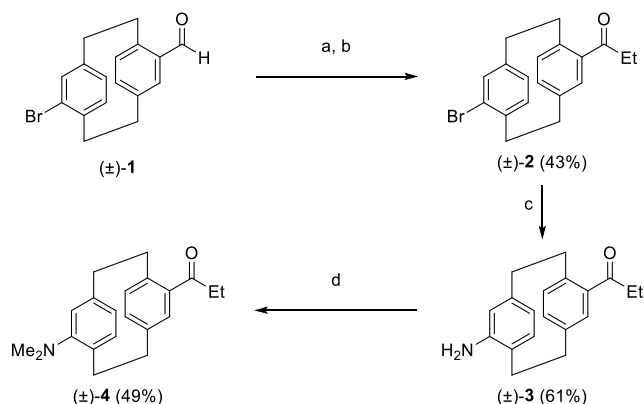
Figure 1. PRODAN and pCp-based analogues

We also describe the spectroscopic properties of these compounds (UV-Vis absorption, fluorescence emission, solvatochromic characteristics), and show that, depending on their substitution pattern, the enantiopure pCp-based PRODAN derivatives may possess promising chiroptical behaviors (electronic and vibrational circular dichroism, circularly polarized luminescence). Theoretical calculations are also reported to shed a complementary light on the observed photophysical processes and chiroptical signature.

RESULTS AND DISCUSSION

Synthetic approach. *Pseudo-para* di-substituted pCp-based PRODAN (\pm)-**4** was prepared first according to the following steps (Scheme 1). Bromo-aldehyde (\pm)-**1**¹³ was submitted to a reaction with ethyl magnesium bromide to access the corresponding secondary alcohol in 68% yield. Oxidation of this molecule with Dess-Martin periodinane (DMP) afforded ketone (\pm)-**2** in 64% yield. A Buchwald-Hartwig coupling in the presence of *tert*-butyl carbamate followed by the deprotection of the Boc group with TFA was successfully employed to access amine (\pm)-**3** in 61% overall yield.

Scheme 1. Synthesis of *pseudo-para* substituted pCp-based PRODAN analogue (\pm)-**4**

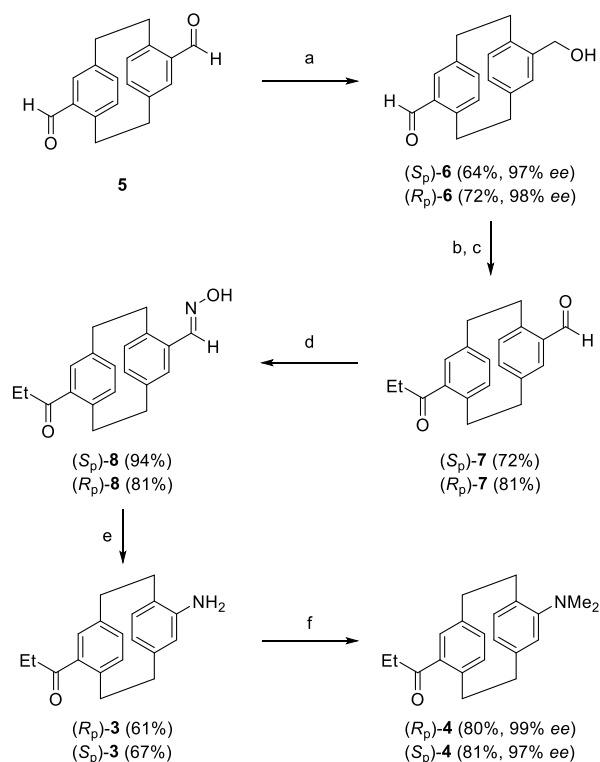


Reaction conditions: a) EtMgBr (1.2 equiv) THF, 0 °C to rt, 4 h; b) DMP (1.2 equiv) THF, rt, 16 h; c) BocNH₂ (3 equiv), PhONa (3.5 equiv) Pd₂dba₃ (1 mol%), JohnPhos (3 mol%) Toluene, 85 °C, 16 h, then TFA (9 equiv) CH₂Cl₂, rt, 16 h; d) MeI (2 equiv) K₂CO₃ (5 equiv), DMF, rt, 24 h.

Methylation under classical conditions with MeI finally led to the desired “through-space” conjugated 3D PRODAN (\pm)-**4**, which was isolated in 49% yield.

To access the two enantiomers of compound **4** we followed a different synthetic approach which relies on a desymmetrization reaction previously developed in our laboratory (Scheme 2).^{10b} Centrosymmetric dialdehyde **5** was submitted to an asymmetric transfer hydrogenation promoted by Noyori’s catalysts (either RuCl(*p*-cymene)[(*S,S*)-Ts-DPEN] or RuCl(*p*-cymene)[(*R,R*)-Ts-DPEN]) and *t*-BuOK in a 1:1 *i*-PrOH/DMF mixture. The resulting enantiopure alcohols (*S_p*)-**6** and (*R_p*)-**6** were first reacted with ethyl magnesium bromide, and then reoxidized with DMP to afford products (*S_p*)-**7** and (*R_p*)-**7** in good overall yields. These derivatives were converted to the corresponding oximes via a condensation reaction with hydroxylamine. Compounds (*S_p*)-**8** and (*R_p*)-**8** were treated with Koser’s reagent^{14,15} to generate the corresponding anilines (*S_p*)-**3** and (*R_p*)-**3** in one step and good yields. *N,N*-dimethylation of the amine function finally led to the desired enantiopure 3D PRODANS (*S_p*)-**4** and (*R_p*)-**4**, which were isolated in high yields.

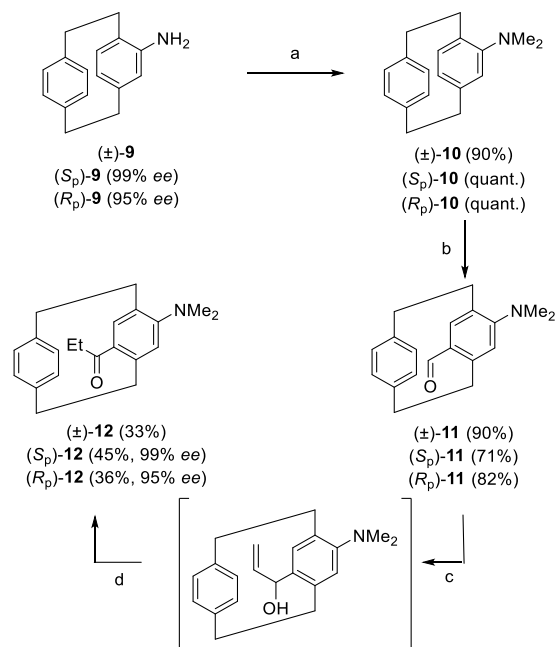
Scheme 2. Synthesis of *pseudo-para* substituted pCp-based PRODAN analogues (*S_p*)-**4** and (*R_p*)-**4**



Reaction conditions: a) RuCl(*p*-cymene)[(*S,S*)-Ts-DPEN] or RuCl(*p*-cymene)[(*R,R*)-Ts-DPEN] (5 mol %), *t*-BuOK (10 mol %), *i*-PrOH/DMF 1:1 (v/v), 0 °C, 70 min; b) EtMgBr (2.4 equiv) THF, 0 °C to rt, 16 h; c) DMP (2.5 equiv.), CH₂Cl₂, rt, overnight; d) H₂NOH·HCl (1.25 equiv), NaOH (1.25 equiv), EtOH, 30 min, 80 °C; e) Koser’s reagent (1.4 equiv), DMSO, rt for 30 min then 80 °C for 1 h, then NaOH (1.5 equiv), 80 °C, 1.5 h; f) MeI (7.5 equiv), K₂CO₃ (5.8 equiv), DMF, rt, 24 h.

Para di-substituted pCp-based Prodan **12** was synthesized starting from 4-amino[2.2]paracyclophane (Scheme 3).¹⁶ Treatment of amine (\pm)-**9**, with paraformaldehyde in acetic acid under reducing conditions afforded the *N,N*-dimethylated compound (\pm)-**10** in 90% yield. This derivative was then submitted to a regioselective Vilsmeier-Haak reaction recently developed in our laboratory.^{10c} At first, the resulting *para*-formylated product (\pm)-**11** was treated with ethyl magnesium bromide. Different oxidizing agents (MnO₂, DMP, DDQ) were next screened to convert the obtained ethyl alcohol into the corresponding ketone derivative. However, no conversion or decomposition of the starting material was observed after each trial. In this case, the presence of an amino group on the molecules probably prevented the reaction from occurring.

Scheme 3. Synthesis *para*-substituted pCp-based Prodan analogues (\pm)-**12**, (*S_p*)-**12**, and (*R_p*)-**12**



Reaction conditions: a) (CH₂O)_n, NaBH₃CN, Acetic acid, 0 °C to rt, 16 h; b) POCl₃, DMF, 0 to 100 °C, 3 h; c) vinylmagnesium bromide (1.0 M in THF), THF, 0 °C to rt, 4 h; d) (PPh₃)₃RuCl₂ (0.05 equiv.), *n*-BuLi (1.6 M in hexane, 0.1 equiv.) dry THF, reflux overnight.

An alternative strategy was therefore implemented to access the desired compound **12** (Scheme 3). This time, aldehyde (\pm)-**11** was reacted with vinylmagnesium bromide to access a vinyl alcohol intermediate (compound in brackets, Scheme 3). A double-bond isomerization¹⁷ in the presence of *n*-BuLi and (PPh₃)₃RuCl₂ finally led to ethyl ketones (\pm)-**12**, which was isolated in 33%. As depicted in Scheme 3, the enantiopure products (*S_p*)-**12** and (*R_p*)-**12** were individually obtained starting from enantiopure amines (*S_p*)-**9** and (*R_p*)-**9** using the same synthetic approach employed to access the racemic compound (\pm)-**12**.

Unpolarized UV-Vis absorption and fluorescence emission. Having the *pseudo-para* and *para* substituted pCp-based derivatives (\pm)-**4** and (\pm)-**12** in hand, we under-

took a photophysical investigation of the impact of the pCp core and its “*phane*” interactions on the spectroscopic properties of these chromophores compared to “classical” PRODAN. When dissolved in dichloromethane (CH₂Cl₂), the absorption and fluorescence maxima of the *para* substituted pCp-based analogue (\pm)-**12** were found to be localized at 350 nm and 437 nm respectively, similarly to what is observed for commercially available PRODAN, the slight blueshift of (\pm)-**12** being the logical consequence of the shorter conjugation path (Figure 2). In contrast, the *pseudo-para* di-substituted derivative (\pm)-**4** showed a blue-shifted absorption spectrum with a weaker band around 328 nm, as well as a redshifted emission peaking at 542 nm (Figure 2). As a result, an extremely large Stokes shift (12038 cm⁻¹) was obtained for this compound. Such an extreme value can be explained by the large geometrical relaxation of the strongly dipolar excited state (see Theoretical calculations below). Both pCp-based chromophores showed low fluorescence quantum yields in dichloromethane (1% and <0.1% for (\pm)-**12** and (\pm)-**4** respectively). The lower quantum yield as compared to the parent PRODAN originates in the increased flexibility of the dyes, and of the related non-radiative pathways. In addition, for (\pm)-**4**, theoretical calculations show that the emitting state becomes much less dipole allowed (largely decreased oscillator strength as compared to both (\pm)-**12** and PRODAN), also indicative of a decreased radiative emission rate.

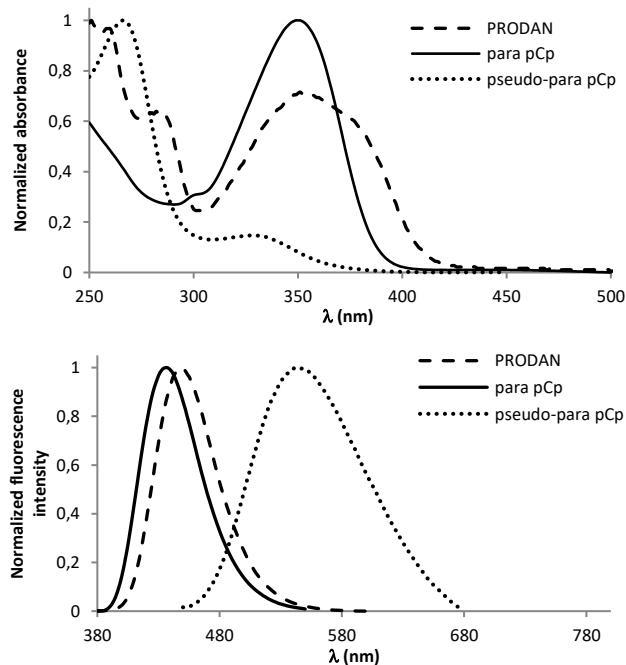
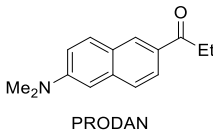
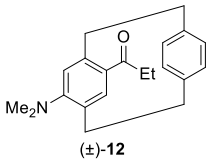
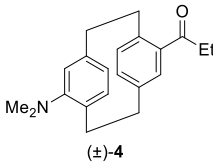


Figure 2. Absorption and emission spectra of PRODAN, *pseudo-para* substituted pCp (\pm)-**4** and *para* substituted pCp (\pm)-**12** (10⁻⁵ M solutions in CH₂Cl₂).

The solvatochromic behavior of compounds (\pm)-**4** and (\pm)-**12** was also examined. (Table 1). As expected, increasing solvent polarity resulted in clear redshifts of the emission spectra for both pCp-based PRODAN analogues (\pm)-**4** and (\pm)-**12**. The *para*-substituted compound (\pm)-**12**

showed a less pronounced solvatochromism in comparison with commercially available PRODAN (34 nm vs 69 nm from toluene to ethanol, Table 1, entries 2 vs 1). The *pseudo-para* substituted derivative (\pm)-**4**, on its side, suffered from fluorescence quenching in acetonitrile and ethanol (Table 1, entry 3). Even so, this chromophore showed emission maxima at 486 nm in toluene and 542 nm in dichloromethane, which resulted in a strong red-shift of its bands (up to 56 nm, Table 1, entry 2).

Table 1. Solvatochromic properties of pCp-based chromophores (\pm)-4** and (\pm)-**12** vs PRODAN**

Entry	Compound	Solvent	λ_{em} (nm) ^a
1 ^b	 PRODAN	toluene	416
		1,4-dioxane	422
		CH ₂ Cl ₂	446
		MeCN	455
		EtOH	485
2	 (\pm)- 12	toluene	424
		1,4-dioxane	425
		CH ₂ Cl ₂	437
		MeCN	440
		EtOH	458
3	 (\pm)- 4	toluene	486
		1,4-dioxane	506
		CH ₂ Cl ₂	542
		MeCN	/
		EtOH	/

a) 1×10^{-5} M solutions of the dyes were used to perform the analyses ($\lambda_{ex} = 350$ nm for both compounds (\pm)-**4** and (\pm)-**12**). Diminished fluorescence intensities were generally observed in polar solvents. b) Fluorescence emissions of commercially available PRODAN has been described before, see ref.18.

Interestingly, the pCp derivative (\pm)-**4** was found to exhibit enhanced fluorescence in the solid state (Figure 3).

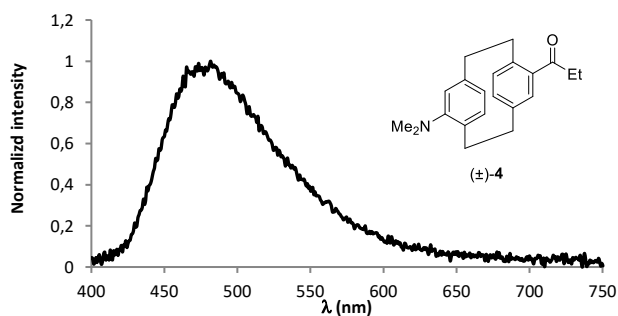


Figure 3. Emission spectra *pseudo-para* substituted pCp (\pm)-**4** at the solid state ($\lambda_{ex} = 360$ nm).

Indeed, when excited at 360 nm, a broad emission band was observed with a maximum at 486 nm. An absolute quantum yield of 9% could be measured. This aggregation-induced emission enhancement effect originates likely from the stiffening occurring in the solid-state which decreases the efficiency of the non-radiative routes. In short our results clearly show that the photophysical properties of the pCp-based PRODAN analogues are strongly influenced by through-space interactions, and can easily be modulated by changing the relative position of the electron-donating and electron-withdrawing groups onto the two aromatic rings of [2.2]paracyclophane.

Theoretical investigations. In order to gain further insights into the photophysics of the “*phane*” compounds, we firstly carried out a benchmark of the exchange-correlation functionals on the commercially available PRODAN probe (see Table S1) and then applied the selected functional, namely ω B97X-D, to the compounds **4** and **12**. In CH₂Cl₂, the *para*-pCp **12** shows similar characteristics as the commercially available PRODAN, (see Figure S4 and Table S5), the first excitation being a $\pi\pi^*$ charge transfer (CT) transition of purely HOMO to LUMO character accompanied by a strong increase of the dipole moment (+4.92 D). For comparisons, in PRODAN, the excitation appears slightly redshifted (+12 nm as compared to **12**), with a slightly larger increase of dipole moment upon excitation (+5.79 D), consistent with the experimental trends. The frontier orbitals of **12** are located, as expected, on the amino-moiety (HOMO) and the ketone (LUMO) hence the electron density difference (EDD) shows no implication of the pCp phenyl on this transition (see Figure 4). When diminishing the solvent polarity, this CT $\pi\pi^*$ state is destabilized thus blueshifted, which results in a state mixing and intensity borrowing with the higher-lying energy $\pi\pi^*$ states (see Table S3) further highlighted by the close shapes of the loss and gain electron density area of the EDDs S₁ and S₂ in 1,4-dioxane (see Figure S3). In CH₂Cl₂, the relaxed CT state lie at 3.19 eV above the ground state, thus an emission at ca. 389 nm is computed (see Table S5), similar to the one of PRODAN. Despite our effort, the intense state mixing prevented us to optimize the excited state geometries in less polar solvent.

As can be seen in Tables S6, S7, and S8, the transitions to the lowest excited states of compound **4** do present small oscillator strengths, and the first intense transition corresponds to the fifth and sixth excited-states in CH₂Cl₂. This explains the blueshift of the absorption band noticed experimentally. In studying emission, we noticed that the two lowest excited states have similar energies at the FC point. As can be seen in Figure 4, The S₁ is a local $\pi\pi^*$ excitation on the keto-bearing phenyl, whereas the S₂ state corresponds to a strong CT between the two ring systems. This is actually the HOMO to LUMO excitation, these two frontier MOs being localized on different cycles (see Figures S7 and S8). This CT excitation induces a large increase in the dipole moment ($\Delta\mu = +6.65$ D in CH₂Cl₂).

When optimizing the two lowest excited states in CH_2Cl_2 , one logically notices a state swapping, the second excitation at the FC point becoming the lowest after geometry relaxation. For **4** the lowest absorbing and emissive states have therefore totally different nature. The extreme experimental Stokes shift recorded in CH_2Cl_2 , explained by this specific feature, is also quantitatively reproduced by the computations. Indeed, the highly-polar fluorescent state is strongly stabilized with an emission computed at 510 nm. This corresponds to a Stokes shift of 12650 cm^{-1} in CH_2Cl_2 , perfectly in line with the measurements. Eventually, we note that the oscillator strength of this state is low ($f=0.011$ as compared to $f=0.431$ in **12**), consistent with the very small emission quantum yield noticed experimentally for **4**.

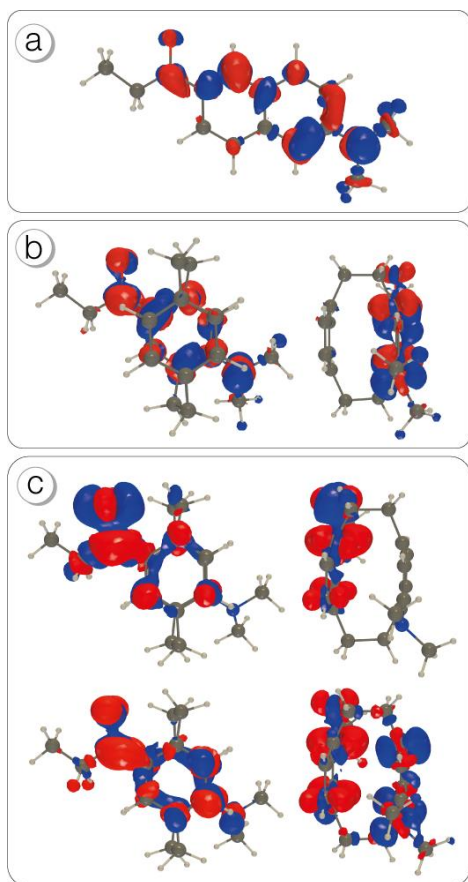


Figure 4. Electron density difference (EDD) plots in CH_2Cl_2 for a) S_1 in PRODAN b) S_1 in **12** c) (top) S_1 in **4** (bottom) S_2 in **4**.

Chiroptical properties. In recent years, planar chiral pCps were found to possess appealing chiroptical properties such as ECD and CPL activity.⁷⁻⁹ The ECD spectra of the $(S_p)/(R_p)$ -**4** and $(S_p)/(R_p)$ -**12** enantiomeric pairs recorded in CH_2Cl_2 are depicted on Figure 5. They display mirror-image relationships. Several ECD-active bands of moderate strength are observed, for example at 250 ($\Delta\epsilon = -18\text{ M}^{-1}\text{ cm}^{-1}$), 272 (+15), 304 (-5), 334 (+2) and 365 nm (-1) for (S_p) -**4** and at 230 ($\Delta\epsilon = -48\text{ M}^{-1}\text{ cm}^{-1}$), 255 (-35), 285 (+9), 322 (+7) and 352 nm (+17) for (S_p) -**12**. Overall the ECD shapes for *para*- and pseudo-*para*-pCp analogues are

different, and the main overall features are reproduced by theory (see Figures S6 and S10).

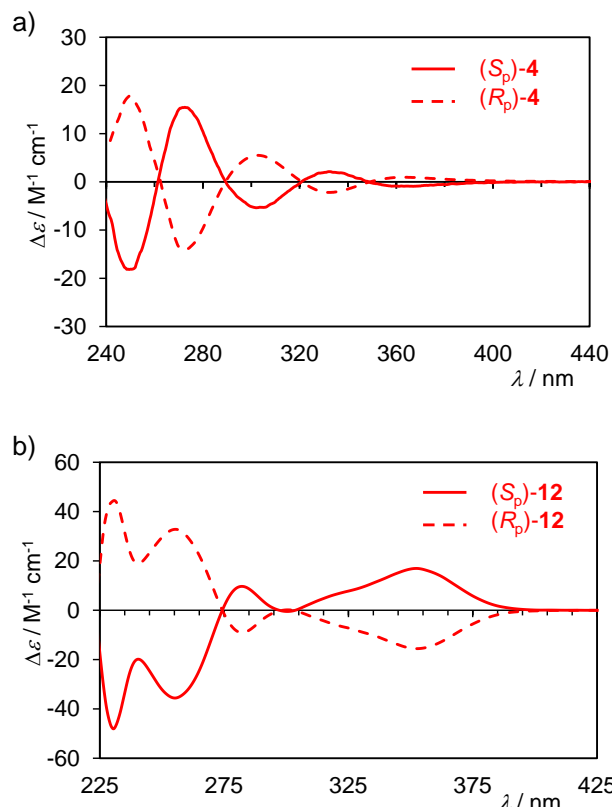


Figure 5. ECD spectra of a) $(S_p)/(R_p)$ -**4** and $(S_p)/(R_p)$ -**12** (CH_2Cl_2 , 10^{-3} M solutions).

The CPL activity of enantioenriched samples of **4** and **12** was also investigated. However, due to the low fluorescence quantum yields, the CPL signals appeared to be difficult to record and only $(S_p)/(R_p)$ -**4** enantiomeric pair in toluene yielded clean mirror-image CPL signatures (Figure 6), with fluorescence dissymmetry factors g_{lum} of $\pm 4 \times 10^{-3}$ ($\lambda_{\text{exc}} = 350\text{ nm}$, $\lambda_{\text{em}} = 486\text{ nm}$, positive signal for the (S_p) enantiomer). These values are in agreement with already reported ones.^{8,19} Note that attempts to measure CPL in solid state failed.

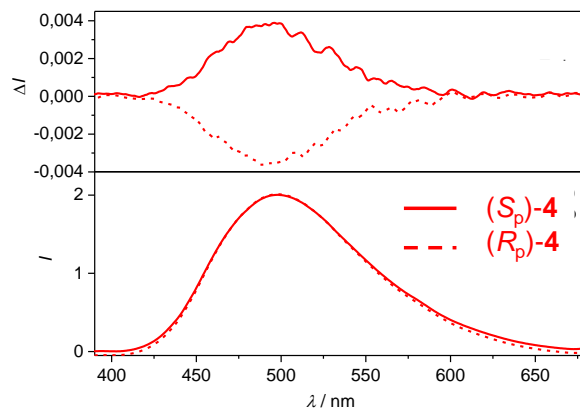


Figure 6. Mirror-image CPL spectra of $(S_p)/(R_p)$ -**4** (toluene, 10^{-5} M).

Another appealing chiroptical spectroscopy for [2.2]pCp derivatives is Vibrational Circular Dichroism (VCD), which may give access to a rich fingerprint in the infrared region and distinguish between different regioisomers.²⁰ Typically, many IR-active bands display either positive or negative signs in VCD and their comparison with DFT calculated spectra can yield important information about conformations and structural features.²¹ Thus, experimental IR and VCD spectra of pseudo-*para* **4** and *para*-pCp **12** enantiomers were measured and compared. Both compounds display a set of several IR-bands of moderate intensity and a strong band around 1655-1675 cm^{-1} for the C=O stretching mode (see Figures 7a, S11 and S12). These features are reproduced by the computations (see Figure S12). While nice experimental mirror-imaged VCD spectra were recorded in CD_2Cl_2 for (*S*_p)/(*R*_p)-**4** (Figure 7b) and displayed several clear fingerprints between 1025 and 1625 cm^{-1} , the ones for (*S*_p)/(*R*_p)-**12** were much less resolved and of much lower intensity (Figure S12), thus highlighting again clear differences between the two regioisomers. Note that the C=O stretching mode was too strong to enable VCD measurements due to saturation.

DFT calculations reveal two conformers for both **4** and **12** depending on the orientation of the carbonyl groups (Figure S2), but the many possible conformations of the ethyl chains were not considered in the DFT calculations. Obviously the Boltzmann-average calculated spectrum closely resembles the experimental ones (compare Figures S12 and S2). The simulated VCD spectra reproduce the key features of (*S*_p)/(*R*_p)-**4** between 1625 to 1025 cm^{-1} and also the ones of (*S*_p)/(*R*_p)-**12** (see Figure S5 and S9) with the correct alternance and shape of positive and negative peaks between 1025 and 1150 cm^{-1} and 1550 to 1625 cm^{-1} .

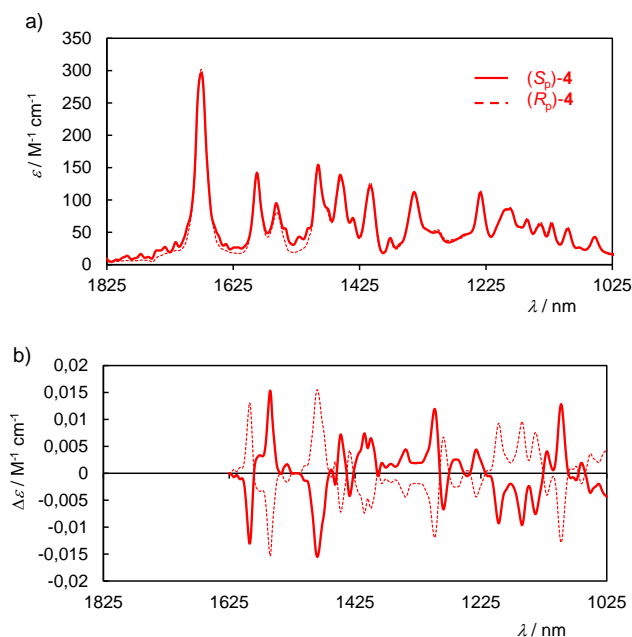


Figure 7. a) IR spectra and b) mirror-image VCD spectra of (*S*_p)/(*R*_p)-**4** (CD_2Cl_2 , 10^{-3} M, 200 microns pathlength).

CONCLUSIONS

In this article we have described the synthesis of differently substituted three-dimensional analogues of PRODAN based on a [2.2]paracyclophane framework. The pCp-based compounds incorporate an electron-donating dimethylamino group and an electron-withdrawing propionyl moiety at their *para* or *pseudo-para* positions. The photophysical properties of the new dyes varied considerably depending on their substitution patterns. The *pseudo-para* derivative **4** revealed an enhanced solvatochromic behaviour in comparison with PRODAN, as well as interesting chiroptical properties both in absorption (ECD or VCD) and emission (CPL, $g_{\text{lum}} = \pm 4 \times 10^{-3}$), despite a low quantum yield of fluorescence. In contrast, the unpolarised UV-Vis absorption and fluorescence emission of the *para* substituted pCp analogue **12** were found to be similar to those of PRODAN, even if a significantly lower quantum yield was observed. Less resolved ECD and VCD spectra were recorded for the pCp-based dye **12**, and no circularly polarised luminescence could be detected. Theoretical investigations were carried out to rationalize the photophysical processes, and confirmed that the lowest absorbing and emissive states of compound **4** have totally different nature, which contrasts with pCp **12**. These findings allow us to conclude that, for this series of dyes, more pronounced solvatochromic and chiroptical behaviours are observed when the two substituents are placed on the two rings of the pCp core in a non “co-planar” arrangement (compound **4**). This work demonstrates that going from a 2D to a 3D structure expands the photophysical space that can be explored by playing with substitution effects. This observation may be particularly useful for the design of new pCp-based luminophores with finely tuned photophysical properties.

EXPERIMENTAL SECTION

General remarks

All reactions were carried out under inert atmosphere, in oven-dried glassware, using dry solvents unless otherwise specified. All commercially available compounds were purchased from Aldrich Chemical Co., Acros Organics or Fisher Scientific and used as received. [2.2]paracyclophane was purchased from Carbosynth, and 4,16-dibromo[2.2]paracyclophane from Alfa Aesar. Analytical thin layer chromatography (TLC) was performed on silica gel plates (Merck 60F254) visualized with a UV lamp (254 nm). Flash chromatography was performed on silica gel (60-230 mesh) unless otherwise specified. Organic extracts were dried over anhydrous MgSO_4 . NMR spectra (^1H and $^{13}\text{C}\{^1\text{H}\}$) were recorded on Bruker Avancell 500 spectrometer, at 500 MHz (H value) in CDCl_3 . Spectra were referenced to residual chloroform (7.26 ppm, ^1H ; 77.0 ppm, $^{13}\text{C}\{^1\text{H}\}$). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), and m (multiplet or overlap of nonequivalent resonances), dd (doublet of doublet), td (triplet of doublet), and br (broad signal). Coupling constants, *J*, are reported in hertz (Hz). DEPT-135 experiments were used to assign ^{13}C NMR spectra. All NMR spectra were obtained at 300K unless otherwise specified. Optical rotations (α_D) were measured on a Perkin Elmer

polarimeter (model 341) at 20 °C. IR spectra were obtained using a spectrum one FT-IR spectrometer (Perkin Elmer). High Resolution mass spectra were recorded on a ThermoFischer Exactive Orbitrap spectrometer. HPLC analyses were performed on a Shimadzu chromatograph equipped with a diode array UV/VIS detector. Absorption and fluorescence spectra were recorded on UV-2700 spectrophotometer (Shimadzu) and F-7000 fluorescence spectrometer (Hitachi), respectively. The photophysical measurements were performed on air-equilibrated solutions, using quartz cuvettes with 1 cm optical path length. Electronic circular dichroism (ECD, in $M^{-1} \text{ cm}^{-1}$) was measured on a Jasco J-815 Circular Dichroism Spectrometer (IFR140 facility - Biosit - Université de Rennes 1). The circularly polarized luminescence (CPL) measurements were performed using a home-built CPL spectrofluoropolarimeter. The samples were excited using a 90° geometry with a Xenon ozone-free lamp 150 W LS. The following parameters were used: emission slit width \approx 2 mm, integration time = 4 sec, scan speed = 50 nm/min, accumulations = 10. The concentration of all the samples was $\sim 10^{-5}$ M (toluene analytical grade) and excitation was performed at 350 nm.

Computational details

DFT calculations are performed using Gaussian16 (ao3p version),²² applying default procedures and algorithms. Geometric and energy convergences are obtained with a tight threshold and an *ultrafine* integration grid is used for ϵ_{xc} . Geometries are optimized with the 6-31+G(d) atomic basis set and the absence of imaginary frequencies is controlled by analytical computation of the Hessian at the same level of theory. Time-Dependent DFT (TD-DFT) calculations use the 6-31+G(2d,p) atomic basis set. The condensed phase studies are performed using the Polarizable Continuum Model (PCM), an implicit solvation model that does not explicitly account for the specific interactions between the solvent and the solute molecules, the latter being placed inside a cavity modelling the polarization of the former. For the TD-DFT part, the present computational protocol also includes corrections linked to the two families of solvent polarization responses, *i.e.*, the Linear Response (LR) and the corrected Linear Response (cLR) which both affect the computed electronic vertical transition, the LR correction providing dispersion-like corrections ($E^{LR} \propto \mu_{tr}$)²³ whereas cLR yields state-specific effects ($E^{cLR} \propto \Delta\mu(ES/GS)$)²⁴ that are crucial to model CT states. The corrections given by these methods can be added together following the equation below where ω_0 is the transition energy obtained through TD-DFT calculations where the solvent does not experience any changes in polarity during the transition.

$$E^{LR+cLR} = E^{LR} + E^{cLR} - \omega_0 \quad (\text{Eq. 1})$$

The IR, VCD and ECD spectrum are computed using the B3LYP functional²⁵ whereas the ω B97-XD functional²⁶ is chosen after a benchmark on the 2D-PRODAN probe (see details in the SI) for the excited states properties, the presence of CT states requiring a range-separated functional. CT parameters are computed using Le Bahers' metrics.²⁷

Synthesis of racemic *pseudo-para* substituted pCp-based PRODAN analogue (\pm)-4

(\pm)-4-Bromo-16-formyl[2.2]paracyclophane (\pm)-1. To a flame-dried 100 mL round-bottomed flask was added *pseudo-para* dibromo[2.2]paracyclophane (0.994 g, 2.72 mmol, 1 equiv.) and dry THF (80 mL). The solution was cooled to -78 °C in a

dry ice/acetone bath and *n*-BuLi (2.5 M, 1.6 mL, 4 mmol, 1.47 equiv.) was added dropwise via syringe turning the mixture yellow. The reaction was stirred for 30 min, and then DMF (1.61 g, 1.7 mL, 22 mmol, 8.09 equiv.) was added turning the mixture colourless. The solution was allowed to warm to rt and stirred overnight. The mixture was then quenched with a saturated aqueous NH_4Cl solution (50 mL). THF was removed under vacuum. The resulting aqueous solution was taken up with CH_2Cl_2 (40 mL) and washed three times with distilled water (30 mL). The organic layer was collected, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: EtOAc/Cy 1:9 to 1.5:8.5) to give (\pm)-1 (510 mg, 1.62 mmol, 60 %) as an amorphous white solid. ^1H NMR (500 MHz, CDCl_3) δ 9.96 (s, 1H), 7.41 (dd, $J = 7.8, 2.0$ Hz, 1H), 6.98 (d, $J = 1.9$ Hz, 1H), 6.56 (dd, $J = 6.9, 4.6$ Hz, 2H), 6.41 (dt, $J = 16.2, 4.7$ Hz, 2H), 4.19 – 4.05 (m, 1H), 3.50 (ddd, $J = 13.3, 10.4, 2.8$ Hz, 1H), 3.26 (ddd, $J = 13.3, 10.4, 5.2$ Hz, 1H), 3.12 (tdd, $J = 13.6, 10.9, 2.4$ Hz, 2H), 3.07 – 2.98 (m, 1H), 2.98 – 2.85 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): δ 192.0 (CH), 142.7 (C), 141.5 (C), 140.1 (C), 138.9 (C), 137.2 (CH), 137.0 (CH), 136.6 (C), 135.2 (CH), 134.0 (CH), 133.7 (CH), 130.7 (CH), 127.3 (C), 35.2 (CH_2), 34.1 (CH_2), 33.1 (CH_2), 32.9 (CH_2) ppm. Spectroscopic data were consistent with the literature data for this compound.¹³

1-{14-Bromotricyclo[8.2.2.2[^]{4,7}]hexadeca-1(12),4,6,10,13,15-hexaen-5-yl}propan-1-ol (\pm)-51. To a flame-dried 100 mL round-bottomed flask under Argon was added (\pm)-1 (500 mg, 1.59 mmol, 1 equiv.) in dry THF (20 mL). The solution was cooled to 0 °C using an ice bath, then EtMgBr (3 M in Et_2O , 0.25 mL, 0.75 mmol, 1.2 equiv.) was added dropwise. The resulting mixture was allowed to warm to rt during 4 h. The solution was then diluted with EtOAc (10 mL) and H_2O (10 mL). The resulting solution was concentrated under reduced pressure. The aqueous phase was extracted with EtOAc (3 \times 20 mL). The combined organic layers were dried over MgSO_4 and gravity filtered. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using Cy/EtOAc (7:3) as the eluent to afford the desired product (\pm)-51 as a 85:15 mixture of diastereomers. The major isomer could be isolated (371 mg, 1.08 mmol, 68 % yield) as an amorphous white solid after a purification by silica gel column chromatography using a less polar eluent (Cy/EtOAc 9:1). ^1H NMR (500 MHz, CDCl_3): δ 7.14 (dd, $J = 7.7, 1.9$ Hz, 1H), 6.69 (dd, $J = 7.8, 1.8$ Hz, 1H), 6.63 (d, $J = 1.8$ Hz, 1H), 6.56 (d, $J = 1.8$ Hz, 1H), 6.46 (d, $J = 7.8$ Hz, 1H), 6.40 (d, $J = 7.7$ Hz, 1H), 4.81 – 4.74 (m, 1H), 3.50 (ddd, $J = 13.2, 10.4, 2.6$ Hz, 1H), 3.41 – 3.31 (m, 1H), 3.23 (ddd, $J = 13.0, 10.4, 5.3$ Hz, 1H), 3.15 – 2.98 (m, 3H), 2.95 – 2.77 (m, 2H), 1.74 (d, $J = 4.4$ Hz, 1H), 1.68 – 1.59 (m, 1H), 1.60 – 1.47 (m, 1H), 0.90 (t, $J = 7.4$ Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): δ 143.4 (C), 141.2 (C), 139.5 (C), 139.1 (C), 137.0 (CH), 134.9 (C), 134.3 (CH), 134.0 (CH), 129.4 (CH), 129.1 (CH), 127.4 (CH), 127.2 (C), 72.8 (CH), 35.3 (CH_2), 33.6 (CH_2), 33.2 (CH_2), 32.9 (CH_2), 32.7 (CH_2), 9.8 (CH_3) ppm. IR (neat): ν 3445, 2962, 2931, 1588, 1542, 1478, 1457, 1435, 1392, 1259, 12224, 1075, 1066, 1047, 1031, 978, 908, 891, 834, 832, 766, 748, 707 cm^{-1} .

1-{14-Bromotricyclo[8.2.2.2[^]{4,7}]hexadeca-1(12),4,6,10,13,15-hexaen-5-yl}propan-1-one (\pm)-2. To a solution of compound (\pm)-51 (300 mg, 0.87 mmol, 1 equiv.) in dry CH_2Cl_2 (5 mL) was added Dess Martin Periodinane (DMP, 462 mg, 1.09 mmol, 1.2 equiv.). The resulting solution was stirred overnight at rt. The reaction was then quenched with a saturated NaHCO_3

solution (5 mL) and diluted with CH₂Cl₂. The two phases were separated and the aqueous phase extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were washed by water (10 mL) and brine (10 mL), dried over MgSO₄, gravity filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using Cy/EtOAc (19:1) as the eluent to afford product (±)-2 (192 mg, 0.56 mmol, 64 % yield) as an amorphous white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.31 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.84 (d, *J* = 1.3 Hz, 1H), 6.56 (s, 1H), 6.54 – 6.46 (m, 2H), 6.31 (d, *J* = 7.8 Hz, 1H), 3.86 (ddd, *J* = 12.3, 10.5, 1.7 Hz, 1H), 3.48 (ddd, *J* = 13.3, 10.5, 2.7 Hz, 1H), 3.31 – 3.13 (m, 2H), 3.02 (dd, *J* = 17.2, 6.4 Hz, 2H), 2.92 – 2.78 (m, 3H), 2.74 – 2.60 (m, 1H), 1.18 (t, *J* = 7.3 Hz, 3H) ppm. ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 203.7 (C), 142.3 (C), 140.7 (C), 139.2 (C), 138.4 (C), 138.0 (C), 137.0 (CH), 135.3 (CH), 134.0 (CH), 133.3 (CH), 132.0 (CH), 129.9 (CH), 126.9 (C), 35.4 (CH₂), 35.0 (CH₂), 34.2 (CH₂), 33.8 (CH₂), 33.2 (CH₂), 8.6 (CH₃) ppm. IR (neat): ν 3034, 2936, 2854, 1674, 1586, 1549, 1477, 1435, 1390, 1380, 1344, 1259, 1233, 1202, 1158, 1032, 982, 908, 863, 843, 764, 750 cm⁻¹. HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₁₉H₂₀O⁷⁹Br 343.0692; Found 343.0697.

1-[14-Aminotricyclo[8.2.2.2]hexadeca-1(12),4,6,10,13,15-hexaen-5-yl]propan-1-one (±)-3. A flame-dried vial was charged with compound (±)-2 (180 mg, 0.53 mmol, 1 equiv.), *tert*-butyl carbamate (186 mg, 1.59 mmol, 3 equiv.), Pd₂dba₃ (4.9 mg, 0.0064 mmol, 1 mol %), JohnPhos (5.1 mg, 0.017 mmol, 3 mol %) and PhONa (218 mg, 1.88 mmol, 3.6 equiv.). The vial was sealed with a septum, then evacuated and re-filled with argon three times through a needle. Dry toluene (1.2 mL) was added via syringe and the resulting solution was heated at 85 °C in an oil bath overnight. The mixture was then cooled to rt and filtered on Celite with EtOAc washings. The filtrate was concentrated under reduced pressure. The crude material was dissolved in dry CH₂Cl₂ (5 mL), and TFA (0.3 mL, 4.04 mmol, 9.2 equiv.) was added. The mixture was stirred at rt overnight. The reaction was quenched by addition of a saturated NaHCO₃ solution (5 mL). The two phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3x10 mL). The combined organic layers were washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified *via* silica gel column chromatography using Cy/EtOAc (7:3) as eluent to afford product (±)-3 (97 mg, 0.35 mmol, 61 % yield) as an amorphous white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.35 (d, *J* = 7.5 Hz, 1H), 6.84 (s, 1H), 6.41 (d, *J* = 7.7 Hz, 1H), 6.16 (d, *J* = 7.7 Hz, 1H), 6.03 (d, *J* = 7.6 Hz, 1H), 5.39 (s, 1H), 3.98 (t, *J* = 11.2 Hz, 1H), 3.48 (br s, 2H), 3.22 – 3.00 (m, 4H), 3.00 – 2.82 (m, 2H), 2.79 – 2.65 (m, 3H), 1.20 (t, *J* = 7.3 Hz, 3H) ppm. ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 203.0 (C), 144.8 (C), 141.5 (C), 141.2 (C), 138.6 (C), 137.3 (C), 134.7 (CH), 134.2 (CH), 133.9 (CH), 130.3 (CH), 124.1 (C), 122.0 (CH), 121.5 (CH), 35.8 (CH₂), 34.2 (CH₂), 33.4 (CH₂), 32.6 (CH₂), 31.4 (CH₂), 8.6 (CH₃) ppm. IR (neat): ν 3672, 3376, 2972, 2924, 2902, 1674, 1629, 1435, 1260, 1066, 1057, 900, 872, 766, 748 cm⁻¹. HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₁₉H₂₂ON 280.1696; Found 280.1697.

1-[14-(Dimethylamino)-tricyclo[8.2.2.2]hexadeca-1(12),4,6,10,13,15-hexaen-5-yl]propan-1-one (±)-4. A round-bottomed flask was charged with compound (±)-3 (22 mg, 0.08 mmol, 1 equiv.) and K₂CO₃ (55 mg, 0.4 mmol, 5 equiv.) in DMF (2 mL) under an argon atmosphere. MeI (23 mg, 0.01 mL, 2 equiv.) was added, and the resulting mixture was

stirred at rt for 24 h before addition of water. The immiscible phases were then separated, and the aqueous phase was extracted with CH₂Cl₂ (3x10 mL). The combined organic layers were washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using Cy/EtOAc (19:1 to 9:1) as eluent to afford (±)-4 (12 mg, 0.039 mmol, 49 %) as an amorphous white solid. ¹H NMR (500 MHz, CDCl₃): δ 6.91 – 6.86 (m, 2H), 6.43 – 6.36 (m, 1H), 6.27 (d, *J* = 7.6 Hz, 1H), 6.14 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.71 (d, *J* = 1.5 Hz, 1H), 4.00 – 3.89 (m, 1H), 3.44 (ddd, *J* = 13.3, 9.6, 3.3 Hz, 1H), 3.18 (ddd, *J* = 13.1, 9.6, 5.7 Hz, 1H), 3.14 – 2.84 (m, 4H), 2.84 – 2.64 (m, 10H), 1.19 (t, *J* = 7.3 Hz, 3H) ppm. ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 203.1 (C), 151.7 (C), 141.2 (C), 140.8 (C), 139.8 (C), 137.6 (C), 135.1 (CH), 134.6 (CH), 133.5 (CH), 131.9 (CH), 130.5 (C), 124.7 (CH), 120.4 (CH), 43.7 (2CH₃), 35.6 (CH₂), 34.5 (CH₂), 34.2 (CH₂), 33.7 (CH₂), 33.5 (CH₂), 8.6 (CH₃) ppm. IR (neat): ν 2937, 2853, 1675, 1586, 1489, 1455, 1411, 1340, 1265, 1234, 996, 907, 860, 764, 739 cm⁻¹. HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₂₁H₂₆NO 308.2009; Found 308.2007. A mono-methylated amine derivative was also isolated as by-product after the reaction (8.6 mg, 0.029 mmol, 37%).

Synthesis of enantioenriched *pseudo-para* substituted pCp-based PRODAN analogues (S_p)-4 and (R_p)-4

4,16-Diformyl[2.2]paracyclophane 5. An oven-dried one-necked round-bottomed flask was charged with commercially available 4,16-dibromo[2.2]paracyclophane (5 g, 13.7 mmol, 1 equiv.). The flask was sealed with a septum, then evacuated and backfilled with argon three times. Dry Et₂O (300 mL) was added and the resulting solution was cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 32.5 mL, 81.2 mmol, 6 equiv.) was added dropwise via syringe. The mixture was allowed to slowly warm up to rt (~ 1 h), stirred for 8 h at rt, then cooled back to 0 °C. Dry DMF (20 mL, 258 mmol, 19 equiv.) was finally added. The reaction was allowed to warm to rt and stirred overnight. A 6N HCl aqueous solution (16 mL) was added and the resulting mixture was stirred at rt for 1 h. The reaction was diluted with distilled water (20 mL), then extracted with CH₂Cl₂ (2x30 mL). The combined organic layers were washed with a saturated aqueous NaHCO₃ solution (2x20 mL) and brine (2x20 mL), then dried over MgSO₄, filtered and concentrated under reduced pressure. Recrystallization from toluene afforded compound 5 in 93% yield (3.35 g, 12.7 mmol) as colorless crystals. ¹H NMR (500 MHz, CDCl₃): δ 9.94 (s, 2H), 7.05 (d, *J* = 1.9 Hz, 2H), 6.64 (dd, *J* = 7.8, 2.0 Hz, 2H), 6.53 (d, *J* = 7.8 Hz, 2H), 4.13 (ddd, *J* = 13.0, 10.4, 2.4 Hz, 2H), 3.29 (ddd, *J* = 13.1, 10.7, 2.3 Hz, 2H), 3.16 (ddd, *J* = 13.3, 10.4, 5.8 Hz, 2H), 3.02 (ddd, *J* = 13.1, 10.7, 5.8 Hz, 2H) ppm. ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 191.9 (2CH), 142.9 (2C), 140.5 (2C), 136.9 (2CH), 136.8 (2C), 136.5 (2CH), 135.2 (2CH), 34.4 (2CH₂), 32.8 (2CH₂) ppm. **Mp** = 240 °C (decomp.). Spectroscopic data were consistent with the literature data for this compound.²⁸

(±)-4-Formyl-16-hydroxymethyl[2.2]paracyclophane(±)-6. An oven-dried one-necked round-bottomed flask was charged with compound 5 (30 mg, 0.11 mmol, 1 equiv.). The flask was sealed with a septum, then evacuated and backfilled with argon three times. A 10:1 mixture of dry MeOH/THF (5 mL) was added, followed by NaBH₄ (2 mg, 0.053 mmol, 0.5 equiv.). The reaction was stirred at rt for 1 h, then diluted with distilled water (10 mL). The resulting aqueous phase was extracted with EtOAc (3x 10 mL). The combined organic

layers were washed with 1N HCl aqueous solution (2x15 mL), distilled water (2x15 mL) and brine (2x15 mL), then dried over MgSO₄, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel using EtOAc/Cy 3:7 to 4:6 as the eluent to afford compound (\pm)-**6** (8 mg, 0.030 mmol, 27% yield) as an amorphous white solid. ¹H NMR (500 MHz, CDCl₃): δ 9.95 (s, 1H), 7.00 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 7.8, 2.0 Hz, 1H), 6.49 (d, J = 7.8 Hz, 1H), 6.46 (s, 1H), 6.39 (d, J = 1.1 Hz, 2H), 4.69 (d, J = 12.9 Hz, 1H), 4.37 (d, J = 12.9 Hz, 1H), 4.09 (ddd, J = 12.9, 10.4, 2.1 Hz, 1H), 3.39 (ddd, J = 13.5, 10.2, 3.2 Hz, 1H), 3.25 – 2.99 (m, 4H), 2.99–2.86 (m, 2H) ppm. ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 191.9 (CH), 143.2 (C), 140.2 (C), 140.0 (C), 139.9 (C), 137.3 (C), 136.8 (C), 136.6 (CH), 135.2 (CH), 134.1 (CH), 133.9 (CH), 132.0 (CH), 131.3 (CH), 64.3 (CH₂), 34.5 (CH₂), 33.8 (CH₂), 33.0 (CH₂), 32.0 (CH₂) ppm. IR (neat): ν 3397, 2953, 2924, 2854, 1674, 1588, 1484, 1462, 1439, 1411, 1224, 1140, 1023, 986, 903, 787, 718 cm⁻¹. HRMS (ESI-Orbitrap) m/z : [M+H]⁺ Calcd for C₁₈H₁₉O₂:267.1380; Found 267.1384. Centrosymmetric 4-16-dihydroxymethyl[2.2]paracyclophane^{10b} (meso compound) was also isolated as a by-product after the reaction (white amorphous solid, 12 mg, 0.045 mmol, 40% yield).

(*S_p*)-**4-Formyl-16-hydroxymethyl[2.2]paracyclophane** (*S_p*)-**6**. An oven-dried one-necked round-bottomed flask was charged with **5** (1 g, 3.78 mmol, 1 equiv.) in a 1:1 mixture of *i*-PrOH and dry DMF (180 mL) under an argon atmosphere (solution A). Another oven-dried one-necked round-bottomed flask was charged with RuCl(*p*-cymene)[(*S,S*)-TsDPEN] (48 mg, 0.076 mmol, 0.02 equiv.) in dry DMF (10 mL) under an argon atmosphere. To this second solution was added *t*-BuOK (42 mg, 0.38 mmol 0.1 equiv.) solubilised in *i*-PrOH (10 mL). After the disappearance of the violet colour, the mixture was added to the solution A. The reaction was stirred at 0 °C for 70 min. The consumption of the starting material was monitored by TLC. The mixture was then quenched with a saturated NH₄Cl aqueous solution. The resulting aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, gravity filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel using Cy/EtOAc (8:2 to 1:1) as eluent to afford the compound (*S_p*)-**6** (647 mg, 2.43 mmol, 64% yield, 97% *ee*) and unreacted **5** (228 mg, 0.86 mmol, 23% yield) as amorphous white solids. [α]_D +135 (c 0.3 CHCl₃).

(*R_p*)-**4-Formyl-16-hydroxymethyl[2.2]paracyclophane** (*R_p*)-**6**. An oven-dried one-necked round-bottomed flask was charged with **5** (1 g, 3.78 mmol, 1 equiv.) in a 1:1 mixture of *i*-PrOH and dry DMF (180 mL) under an argon atmosphere (solution A). Another oven-dried one-necked round-bottomed flask was charged with RuCl(*p*-cymene)[(*R,R*)-TsDPEN] (48 mg, 0.076 mmol, 0.02 equiv.) in dry DMF (10 mL) under an argon atmosphere. To this second solution was added *t*-BuOK (42 mg, 0.38 mmol 0.1 equiv.) solubilised in *i*-PrOH (10 mL). After the disappearance of the violet colour, the mixture was added to the solution A. The reaction was stirred at 0 °C for 75 min. The consumption of the starting material was monitored by TLC. The mixture was then quenched with a saturated NH₄Cl aqueous solution. The resulting aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, gravity filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel using Cy/EtOAc (8:2 to 1:1) as eluent

to afford the compound (*R_p*)-**6** (727 mg, 2.73 mmol, 72% yield, 98% *ee*) as an amorphous white solid. [α]_D –100 (c 0.3 CHCl₃).

(*S_p*)-**11-Propanoyltricyclo[8.2.2.2[^]{4,7}]hexadeca-1(12),4(16),5,7(15),10,13-hexaene-5-carbaldehyde** (*S_p*)-**7**. A round-bottomed flask was charged compound (*S_p*)-**6** (300 mg, 1.13 mmol, 1 equiv.) in THF (22 mL) under an argon atmosphere. The resulting solution was cooled to 0 °C, and EtMgBr (3 M in Et₂O, 1.5 mL, 4.50 mmol, 4 equiv.) was added dropwise by syringe. The resulting mixture was allowed to warm to rt. After stirring at rt for 16 h, the solution was quenched by the addition of H₂O (20 mL). The resulting solution was concentrated under reduced pressure to remove THF. The aqueous phase was then extracted with EtOAc (3x20 mL). The combined organic layers were washed by brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude material was then dissolved in dry CH₂Cl₂ (20 mL), and DMP (1.179 g, 2.78 mmol, 2.5 equiv.) was added. The mixture was stirred at rt overnight. The reaction was quenched by the addition of a saturated NaHCO₃ solution (15 mL). The two phases were separated and the aqueous solution was extracted with CH₂Cl₂ (3x20 mL). The combined organic layers were washed by brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using Cy/EtOAc (9:1) as the eluent to afford compound (*S_p*)-**7** (237 mg, 0.81 mmol, 72% yield) as an amorphous white solid. ¹H NMR (500 MHz, CDCl₃): δ 9.94 (s, 1H), 7.04 (d, J = 1.5 Hz, 1H), 6.87 (s, 1H), 6.78 (dd, J = 7.8, 1.7 Hz, 1H), 6.55 (dd, J = 7.8, 1.5 Hz, 1H), 6.44 (t, J = 7.8 Hz, 2H), 4.12 (ddd, J = 13.0, 10.1, 2.8 Hz, 1H), 3.80 (ddd, J = 12.6, 10.6, 2.0 Hz, 1H), 3.33 (ddd, J = 12.8, 10.5, 5.6 Hz, 1H), 3.25 – 3.09 (m, 3H), 3.04 – 2.78 (m, 3H), 2.64 (dq, J = 17.2, 7.3 Hz, 1H), 1.18 (t, J = 7.3 Hz, 3H) ppm. ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 204.1 (CH), 192.2 (C), 142.6 (C), 141.2 (C), 140.6 (C), 139.7 (C), 138.2 (C), 136.6 (CH et C), 136.1 (CH), 135.3 (CH), 135.2 (CH), 135.0 (CH), 132.5 (CH), 34.9 (CH₂), 34.5 (CH₂), 34.4 (CH₂), 34.1 (CH₂), 32.7 (CH₂), 8.6 (CH₃) ppm. IR (neat): ν 3726, 2933, 2853, 2726, 2300, 1681, 1591, 1553, 1460, 1343, 1276, 1251, 1231, 1144, 1009, 968, 901, 879, 846, 764, 749 cm⁻¹. HRMS (ESI-Orbitrap) m/z : [M+H]⁺ Calcd for C₂₀H₂₁O₂ 293.1536; Found 293.1532.

[α]_D –56 (c 0.1 CHCl₃).

(*R_p*)-**11-Propanoyltricyclo[8.2.2.2[^]{4,7}]hexadeca-1(12),4(16),5,7(15),10,13-hexaene-5-carbaldehyde** (*R_p*)-**7**. This compound was prepared following the procedure described for the synthesis of product (*S_p*)-**7**: (*R_p*)-**6** (250 mg, 0.94 mmol, 1 equiv.), EtMgBr (3 M in Et₂O, 1.25 mL, 3.75 mmol, 4 equiv.) in THF (18 mL), then DMP (903 mg, 2.13 mmol, 2.5 equiv.) in CH₂Cl₂ (25 mL). The crude product was purified by silica gel column chromatography (EtOAc/Cy 1:9) to afford the compound (*R_p*)-**7** (200 mg, 0.68 mmol, 81% yield) as an amorphous white solid. [α]_D +66 (c 0.1 CHCl₃).

(*S_p*)-**1-[14-[(1*E*)-(hydroxyimino)methyl]tricyclo[8.2.2.2[^]{4,7}]hexadeca-1(12),4,6,10,13,15-hexaen-5-yl]propan-1-one** (*S_p*)-**8**. To a mixture of hydroxylamine hydrochloride (0.072 g, 1.03 mmol, 1.3 equiv.) and NaOH (0.042 g, 1.05 mmol, 1.3 equiv.) in ethanol (5 mL) at reflux was added a solution (*S_p*)-**7** (0.230 g, 0.79 mmol, 1.0 equiv.) in EtOH (10 mL). The resulting mixture was heated at reflux in an oil bath for 30 min. The reaction was then cooled to rt, and the solvent was evaporated under reduced pressure. The residue was taken up with EtOAc (20

mL). The organic layer was washed with H₂O (2x15 mL), and brine (20 mL), then dried over MgSO₄. Evaporation of the solvent afforded the desired product (*S_p*)-**8** as a colourless solid (227 mg, 0.74 mmol, 94% yield). ¹H NMR (500 MHz, CDCl₃): δ 8.17 (s, 1H), 7.36 (s, 1H), 6.88 (s, 1H), 6.81 (s, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 7.7 Hz, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 3.84 (t, *J* = 11.5 Hz, 1H), 3.58 (ddd, *J* = 13.0, 10.2, 2.6 Hz, 1H), 3.28 – 3.19 (m, 1H), 3.10 (ddd, *J* = 9.5, 7.2, 4.2 Hz, 3H), 2.96 – 2.81 (m, 3H), 2.72 – 2.62 (m, 1H), 1.19 (t, *J* = 7.3 Hz, 3H) ppm. ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 203.8 (C), 149.7 (CH), 141.0 (C), 140.8 (C), 139.3 (C), 138.8 (C), 138.1 (C), 135.2 (CH), 134.3 (CH), 134.0 (CH), 132.9 (CH), 132.4 (CH), 131.9 (C), 131.6 (CH), 35.2 (CH₂), 34.5 (CH₂), 34.4 (CH₂), 33.9 (CH₂), 33.0 (CH₂), 8.6 (CH₃) ppm. IR (neat): ν 3378, 2969, 1738, 1455, 1365, 1216, 1016, 872, 748 cm⁻¹. HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₂₀H₂₂NO₂ 308.1645; Found 308.1636. [α]_D –193 (c 0.17 CHCl₃).

(*R_p*)-1-[14-[(1*E*)-(hydroxyimino)methyl]tricyclo[8.2.2.2^{4,7}]hexadeca-1(12),4,6,10,13,15-hexaen-5-yl]propan-1-one (*R_p*)-**8**. This compound was prepared following the procedure described for the synthesis of product (*S_p*)-**8**: (*R_p*)-**7** (185 mg, 0.63 mmol, 1 equiv.), hydroxylamine hydrochloride (0.055 g, 0.80 mmol, 1.25 equiv.), and NaOH (0.032 g, 0.79 mmol, 1.25 equiv.) in EtOH (10 mL). The crude product was purified by silica gel column chromatography (EtOAc/Cy 1:9) to afford compound (*R_p*)-**8** (158 mg, 0.51 mmol, 81% yield) as an amorphous white solid. [α]_D + 195 (c 0.09 CHCl₃).

(*R_p*)-1-[14-aminotricyclo[8.2.2.2^{4,7}]hexadeca-1(12),4,6,10,13,15-hexaen-5-yl]propan-1-one (*R_p*)-**3**. A mixture of finely ground (*S_p*)-**8** (52 mg, 0.17 mmol, 1.0 equiv.) and finely ground Koser's reagent¹⁵ (96 mg, 0.24 mmol, 1.45 equiv.) in DMSO (2 mL) was stirred at rt for 30 min and then heated to 80 °C in an oil bath for 1 h. Finely ground NaOH (10 mg, 0.25 mmol, 1.5 equiv.) was added and the heating continued for 1.5 h. The mixture was then cooled to rt and H₂O (10 mL) added. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H₂O (2x10 mL), and brine (15 mL) then dried over MgSO₄. The solvent was removed under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (EtOAc/Cy 1:9) to isolate the desired product (*R_p*)-**3** as a colorless solid (29 mg, 0.10 mmol, 61% yield). [α]_D – 61 (c 0.1 CHCl₃).

(*S_p*)-1-[14-aminotricyclo[8.2.2.2^{4,7}]hexadeca-1(12),4,6,10,13,15-hexaen-5-yl]propan-1-one (*S_p*)-**3**. This compound was prepared following the procedure described for the synthesis of product (*R_p*)-**3**: (*R_p*)-**8** (50 mg, 0.16 mmol, 1 equiv.), Koser's reagent (89 mg, 0.23 mmol, 1.4 equiv.), and NaOH (10 mg, 0.24 mmol, 1.5 equiv.) in DMSO (2 mL). The crude product was purified by silica gel column chromatography (EtOAc/Cy 1:9) to afford compound (*S_p*)-**3** (30 mg, 0.11 mmol, 67% yield) as an amorphous white solid. [α]_D + 60 (c 0.04 CHCl₃).

(*R_p*)-1-[14-(Dimethylamino)tricyclo[8.2.2.2^{4,7}]hexadeca-1(12),4,6,10,13,15-hexaen-5-yl]propan-1-one (*R_p*)-**4**. This compound was prepared following the procedure described above for the synthesis of racemic product (±)-**4**: (*R_p*)-**3** (21 mg, 0.08 mmol, 1 equiv.), MeI (80 mg, 0.035 mL, 7.5 equiv.), and K₂CO₃ (60 mg, 0.43 mmol, 5.8 equiv.) in DMF (1.8 mL) under an argon atmosphere. The crude product was purified by silica gel column chromatography (EtOAc/Cy 1:9 to 1:9) to afford compound (*R_p*)-**4** (18 mg, 0.06 mmol, 80% yield,

99% *ee*) as an amorphous white solid. [α]_D –136 (c 0.06 CHCl₃).

(*S_p*)-1-[14-(Dimethylamino)tricyclo[8.2.2.2^{4,7}]hexadeca-1(12),4,6,10,13,15-hexaen-5-yl]propan-1-one (*S_p*)-**4**. This compound was prepared following the procedure described above for the synthesis of racemic product (±)-**4**: (*S_p*)-**3** (21 mg, 0.08 mmol, 1 equiv.), MeI (68 mg, 0.03 mL, 6.4 equiv.), and K₂CO₃ (55 mg, 0.40 mmol, 5.3 equiv.) in DMF (2 mL) under an argon atmosphere. The crude product was purified by silica gel column chromatography (EtOAc/Cy 1:9 to 1:9) to afford compound (*S_p*)-**4** (19 mg, 0.06 mmol, 81% yield, 97% *ee*) as an amorphous white solid. [α]_D + 120 (c 0.05 CHCl₃).

Synthesis of racemic and enantioenriched *para* substituted pCp-based PRODAN analogues (±)-**12**, (*S_p*)-**12**, and (*R_p*)-**12** (±)-**4**-Dimethylamino[2.2]paracyclophane (±)-**10**. To a degassed solution of 4-amino[2.2]paracyclophane (±)-**9**⁶ (1 eq., 742 mg, 3.3 mmol) in AcOH (22 mL) at room temperature, paraformaldehyde (10 eq., 998 mg, 33.2 mmol) followed by NaBH₃CN (5 eq., 981 mg, 15.7 mmol) were added. The reaction was stirred overnight at rt. The mixture was poured into an ice cold 1M NaOH solution (30 mL) and stirred for 30 min. The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with water (50 mL), and brine (50 mL), then dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified via silica gel column chromatography (eluent = pentane/CH₂Cl₂ 1:1) to afford compound (±)-**10** (751 mg, 2.9 mmol, 90 %) as an amorphous white solid. ¹H NMR (500 MHz, CDCl₃) δ 6.73 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.53 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.44 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.42 – 6.34 (m, 2H), 6.22 (dd, *J* = 7.6, 1.4 Hz, 1H), 5.65 (d, *J* = 1.3 Hz, 1H), 3.43 (ddd, *J* = 13.5, 9.1, 2.4 Hz, 1H), 3.12 (ddd, *J* = 12.9, 9.0, 7.2 Hz, 1H), 3.07 – 2.85 (m, 5H), 2.81 – 2.63 (m, 7H) ppm. ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 151.4 (C), 140.8 (C), 139.9 (C), 138.7 (C), 136.3 (CH), 132.9 (CH), 132.6 (CH), 131.2 (CH), 130.8 (C), 128.7 (CH), 125.7 (CH), 121.0 (CH), 43.4 (2CH₃), 35.5 (CH₂), 35.3 (CH₂), 35.2 (CH₂), 33.9 (CH₂) ppm. Spectroscopic data were consistent with the literature data for this compound.²⁹

(*S_p*)-**4**-Dimethylamino[2.2]paracyclophane (*S_p*)-**10**. This compound was prepared following the procedure described for the synthesis of product (±)-**10**: (*S_p*)-**9**^{10e} (72 mg, 0.32 mmol, 99% *ee*, 1 equiv.), AcOH (3 mL), paraformaldehyde (99 mg, 3.2 mmol, 10 equiv.), NaBH₃CN (95 mg, 1.5 mmol, 5 equiv.), rt, overnight. The crude product was purified via silica gel column chromatography (eluent = pentane/CH₂Cl₂ 1:1) to afford compound (*S_p*)-**10** (80 mg, 0.32 mmol, quant. yield) as an amorphous white solid. [α]_D + 192 (c 0.05 CHCl₃).

(*R_p*)-**4**-Dimethylamino[2.2]paracyclophane (*R_p*)-**10**. This compound was prepared following the procedure described for the synthesis of product (±)-**10**: (*R_p*)-**9**^{10e} (130 mg, 0.58 mmol, 1 equiv., 95% *ee*), paraformaldehyde (175 mg, 5.21 mmol, 10 equiv.), and NaBH₃CN (172 mg, 2.74 mmol, 4.7 equiv.) in AcOH (4 mL) under an argon atmosphere. The crude product was purified by silica gel column chromatography (eluent = pentane/CH₂Cl₂ 1:1) to afford compound (*R_p*)-**10** (145 mg, 0.57 mmol, quant. yield) as an amorphous white solid. [α]_D – 213 (c 0.05 CHCl₃).

(±)-**4**-Dimethylamino-7-formyl[2.2]paracyclophane (±)-**11**. In a 25 mL flame and vacuum dried-round bottomed flask, POCl₃ (1 eq., 345 mg, 0.2 mL, 2.25 mmol) was added dropwise to vigorously stirred DMF (2 mL) at 0 °C, under argon atmosphere. After 15 min, a solution of compound (±)-**10** (1 eq., 565 mg, 2.25 mmol) in DMF (10 mL) was added dropwise. After

another 15 min, the resulting green solution was allowed to warm back to rt and stirred for 1h. The reaction was then heated to 100 °C in an oil bath, and stirred for an additional 2h. The mixture was then poured into ice and water under vigorous stirring. Sat'd aq. NaOAc solution was added until a basic solution was obtained (pH~8). CH₂Cl₂ was added and the immiscible phases were separated. The aqueous phase was extracted several times with CH₂Cl₂, until yellow colour faded. The organic phases were then combined, washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified via silica gel column chromatography (eluent = Cy/EtOAc 9:1) to afford compound (±)-**11** (565 mg, 2.02 mmol, 90%) as an amorphous pale yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 9.80 (s, 1H), 6.94 (s, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.44 (q, *J* = 7.9 Hz, 2H), 5.56 (s, 1H), 4.10 – 3.90 (m, 1H), 3.37 (dd, *J* = 13.3, 7.4 Hz, 1H), 3.27 – 3.09 (m, 2H), 3.05 – 2.99 (m, 1H), 2.93 (s, 6H), 2.88 – 2.64 (m, 3H) ppm. ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 190.0 (CH), 155.4 (C), 145.5 (C), 141.2 (C), 139.4 (C), 138.6 (C), 132.3 (CH), 131.8 (CH), 130.5 (CH), 129.0 (CH), 127.2 (C), 122.4 (CH), 42.3 (2CH₃), 37.2 (CH₂), 35.2 (CH₂), 33.5 (CH₂), 33.2 (CH₂) ppm. IR (neat): ν 2925, 1702, 1667, 1581, 1530, 1503, 1438, 1412, 1356, 1314, 1260, 1230, 1209, 1157, 1070, 912, 374, 810, 744 cm⁻¹. HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₁₉H₂₂ON 280.1696; Found 280.1693.

(S_p)-4-Dimethylamino[2.2]paracyclophane (S_p)-**11**. This product was prepared following the procedure described for the synthesis of compound (±)-**11**: (S_p)-**10** (75 mg, 0.30 mmol, 1 equiv.), POCl₃ (46 mg, 0.03 mL, 0.30 mmol, 1 equiv.), and DMF (2.5 mL). The crude product was purified by silica gel column chromatography (eluent = Cy/EtOAc 9:1) to afford compound (S_p)-**11** (59 mg, 0.21 mmol, 71%) as an amorphous pale yellow solid. [α]_D + 750 (c 0.01 CHCl₃)

(R_p)-4-Dimethylamino[2.2]paracyclophane (R_p)-**11**. This product was prepared following the procedure described for the synthesis of compound (±)-**11**: (R_p)-**10** (130 mg, 0.52 mmol, 1 equiv.), POCl₃ (0.048 mL, 0.52 mmol, 1 equiv.), and DMF (4 mL). The crude product was purified by silica gel column chromatography (eluent = Cy/EtOAc 9:1) to afford compound (R_p)-**11** (118 mg, 0.42 mmol, 82% yield) as an amorphous pale yellow solid. [α]_D – 1132 (c 0.03 CHCl₃).

Racemic 1-[15-(Dimethylamino)tricyclo[8.2.2.2^{4,7}]hexadeca-1(12),4(16),5,7(15),10,13-hexaen-5-yl]propan-1-one (±)-**12**. Aldehyde (±)-**11** (100 mg, 0.36 mmol, 1 equiv.) was dissolved in dry THF (12 mL) under an argon atmosphere. The solution was cooled to 0 °C, then vinylmagnesium bromide (1 M in THF, 0.54 mL, 0.54 mmol, 1.5 equiv.) was added. The mixture was allowed to warm back to rt and stirred for 2 h. The reaction was then quenched by the addition of a saturated NH₄Cl aqueous solution (20 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product (90 mg, 0.29 mmol, 1 equiv.) was dissolved in dry THF (2 mL). The resulting solution was added to a previously prepared mixture of (PPh₃)₃RuCl₂ (15 mg, 0.015 mmol, 0.05 equiv.) and *n*-BuLi (1.6 M solution in hexane, 24 μL, 0.029 mmol, 0.1 equiv.) in dry THF (0.5 mL), at room temperature, and under an argon atmosphere. The reaction was heated at reflux in an oil bath and stirred overnight. The mixture was then cooled back to rt and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (eluent = pentane/Et₂O 9:1) to isolate product (±)-

12 (36 mg, 0.12 mmol, 33% overall yield) as a yellow amorphous solid. ¹H NMR (500 MHz, CDCl₃): δ 6.90 (s, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 7.9 Hz, 1H), 5.56 (s, 1H), 4.11 – 3.96 (m, 1H), 3.40 (dd, *J* = 14.0, 8.4 Hz, 1H), 3.19 – 3.09 (m, 3H), 2.98 – 2.78 (m, 8H), 2.77 – 2.54 (m, 3H), 1.19 (t, *J* = 7.3 Hz, 3H) ppm. ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 201.5 (C), 154.0 (C), 144.1 (C), 139.7 (C), 139.2 (C), 138.8 (CH), 131.8 (CH), 131.3 (CH), 130.5 (CH), 130.2 (C), 129.0 (CH), 127.0 (C), 123.3 (CH), 42.5 (2CH₃), 37.1 (CH₂), 36.2 (CH₂), 34.7 (CH₂), 33.3 (CH₂), 33.0 (CH₂), 9.0 (CH₃) ppm. IR (neat): ν 2932, 2850, 2792, 1659, 1582, 1528, 1355, 1234, 1098, 1060, 913, 865, 789, 730 cm⁻¹. HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₂₁H₂₆NO 308.2009; Found 308.2004.

(S_p)-1-[15-(Dimethylamino)tricyclo[8.2.2.2^{4,7}]hexadeca-1(12),4(16),5,7(15),10,13-hexaen-5-yl]propan-1-one (S_p)-**12**. Following the procedure described for the synthesis of compound (±)-**12**: (S_p)-**11** (55 mg, 0.20 mmol, 1 equiv.), vinylmagnesium bromide (1 M in THF, 0.30 mL, 0.30 mmol, 1.5 equiv.), and dry THF (7 mL). Then crude compound (60 mg, 0.20 mmol, 1 equiv.), (PPh₃)₃RuCl₂ (9 mg, 0.01 mmol, 0.05 equiv.), and *n*-BuLi (1.4 M solution in hexane, 14 μL, 0.019 mmol, 0.1 equiv.) in dry THF (1.5 mL). The residue was purified by silica gel column chromatography (eluent = pentane/Et₂O 9:1) to afford compound (S_p)-**12** (27 mg, 0.09 mmol, 45% overall yield) as an amorphous white solid. [α]_D + 394 (c 0.05 CHCl₃).

(R_p)-1-[15-(Dimethylamino)tricyclo[8.2.2.2^{4,7}]hexadeca-1(12),4(16),5,7(15),10,13-hexaen-5-yl]propan-1-one (R_p)-**12**. This product has been prepared following the procedure described for the synthesis of compound (±)-**12**: (R_p)-**11** (110 mg, 0.39 mmol, 1 equiv.), vinylmagnesium bromide (1 M in THF, 0.59 mL, 0.59 mmol, 1.5 equiv.), and dry THF (14 mL). Then crude compound (83 mg, 0.27 mmol, 1 equiv.), (PPh₃)₃RuCl₂ (12 mg, 0.013 mmol, 0.05 equiv.), and *n*-BuLi (1.5 M solution in hexane, 18 μL, 0.027 mmol, 0.1 equiv.) in dry THF (2 mL). The residue was purified by silica gel column chromatography (eluent = pentane/Et₂O 9:1) to afford compound (R_p)-**12** (30 mg, 0.098 mmol, 36% overall yield) as an amorphous white solid. [α]_D – 383 (c 0.06 CHCl₃).

ASSOCIATED CONTENT

Supporting Information. HPLC chromatograms of enantiomer-enriched compounds; absorption and emission spectra; IR and VCD spectra; theoretical data; ¹H NMR and ¹³C NMR spectra of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>

AUTHOR INFORMATION

Corresponding Author

* E-mail: erica.benedetti@parisdescartes.fr;
laurent.micouin@parisdescartes.fr;
jeanne.crassous@univ-rennes1.fr;
Denis.Jacquemin@univ-nantes.fr;

Tel: +33 (0)1 76 53 43 07

+33 (0)2 23 23 57 09

+33 (0)2 51 12 55 64

Author Contributions

The manuscript was written through contributions of all authors

Notes

The authors declare no competing financial interest.

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