Diastereoselective Total Synthesis of (+)-Raputindole A: An Iridium-Catalyzed Cyclization Approach

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Submitted date: 28/05/2020 • Posted date: 29/05/2020
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Citation information: Pilli, Ronaldo; Lira Luna Freire Regueira, Juliana; Jr., Luiz Fernando Silva (2020): Diastereoselective Total Synthesis of (+)-Raputindole A: An Iridium-Catalyzed Cyclization Approach. ChemRxiv. Preprint. https://doi.org/10.26434/chemrxiv.12384044.v1

This work describes the total synthesis of Raputindole A (1) through a convergent approach which features: 1) an iridium-catalyzed cyclization to assemble the tricyclic core of the northern part, 2) enzymatic resolution to secure the preparation of enantiomerically pure benzylic alcohol, 3) installation of the butenyl substituent via methallylation of the corresponding benzylic carbocation and coupling of the northern and southern parts via Heck reaction. (+)-Raputindole A (1) was prepared in 10 steps (LLS) and 10% overall yield.

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Diastereoselective Total Synthesis of (+)-Raputindole A: An Iridium-Catalyzed Cyclization Approach

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ABSTRACT: This work describes the total synthesis of Raputindole A (1) through a convergent approach which features: 1) an iridium-catalyzed cyclization to assemble the tricyclic core of the northern part, 2) enzymatic resolution to secure the preparation of enantiomerically pure benzylic alcohol, 3) installation of the butenyl substituent via methallylation of the corresponding benzylic carbocation and coupling of the northern and southern parts via Heck reaction. (+)-Raputindole A (1) was prepared in 10 steps (LLS) and 10% overall yield.

Raputindole A (1) was isolated in 2010, along with three isomers 2-4, from Raputia simullans kalunki, a tree found in the Peruvian amazon rainforest, and displayed moderate activity in the inhibition of CDK2, GSK-3B and DYRK1 kinases (IC50 > 10 uM)12. (figure 1).1 Deoxiraputindole C 5 is another member of this class isolated from Raputia praetermissa.2 Structurally, this is a rare new class of indole alkaloids as it features unsubstituted N1, C2- and C3 positions.3 Other natural products containing this 1,2,3-unsubstituted pattern are trinkentrin A3 and the herbindole family4. Another feature of this rare alkaloid class is the presence of a linear tricyclic scaffold composed by an indane moiety fused to an indole ring as in shearinine D5 and in (+)-nodulisporic acid A.6 A third structural feature of raputindole A (1) is the presence of a bis-prenylated bisindole core as in the antimalarial alkaloids flinderoles A-C7 which can conceivably be traced back to the cyclization of two isoprenyl groups. Other examples of bisindole alkaloids include the spongamine A8, caulindoles9 and dragmacidin D10 which, unlike raputindoles, have their indole moieties connected via C-3 (spongamine A and dragmacidin D) or via C-5 (caulindoles).11 In fact, the raputindoles attracted the attention of the natural products practioners.11
The absolute stereochemistry of raputindole A was determined in 2017 with the first total synthesis accomplished by Lindel and coworkers. Their synthetic route involved an Au(I)-catalyzed cyclization to access the linear tricycle and a Pd-catalyzed installation of the isobutenyl side chain. However, low diastereoselectivity was observed in the indene catalytic hydrogenation to install the stereogenic center at C-7 and to solve this critical step, in 2018, the same group published a diastereoselective total synthesis of raputindole A (1). In addition to the Au(I)-catalyzed assembly of the cyclopenta[n]indole moiety, this second approach featured an iridium-catalyzed asymmetric hydrogenation of the indene double bond guided by a preinstalled hydroxyl function, a Suzuki-Miyaura cross coupling to join the two indole moieties and the final oxidation of the indoline precursor.

Our total synthesis of raputindole A (1) aimed to avoid the use of an indole as a surrogate of the indole ring as it would require a late stage oxidation and of an indene intermediate as the precursor of the stereogenic center at C-7 to prevent the problems previously faced by Lindel and coworkers. Our strategy features the use of N-tosyl indoles in the northern and southern parts of the structure, an iridium-catalyzed diastereoselective cyclization and a Heck cross coupling reaction to build the raputindole A (1) scaffold. It is noteworthy that our approach allows for the incorporation of an enzymatic resolution step which allows to obtain (+)-raputindole A (1).

Our disconnection relies on a convergent approach where the northern and southern parts are connected via a Heck coupling reaction (scheme 1). The isobutenyl side chain would be installed by allylation of tricyclic alcohol 6 with allyltrimethylsilane. The northern part would come from boroindole 7, to be prepared from commercially available bromoindole 8. An iridium-catalyzed cyclization with isoprene would provide linear tricyclic indole 6, according to the methodology described by Hayashi and coworkers for representative boronic acids. The southern part required the preparation of indole 9 via a Batcho-Leimgruber protocol. This convergent approach could also allow for the total syntheses of raputindole B and deoxiraputindole C as well.

**Scheme 1. Retrosynthetic analysis of Raputindole A (1).**

Commercially available 5,6-substituted indole 8 was protected as the corresponding N-tosyl derivative in order to 8 en route to aldehyde 10 which involved N-tosylation, DIBAL-H reduction of the methyl ester and benzylic oxidation with manganese dioxide (3 steps, 95% overall yield) (scheme 2). At this stage, to install the necessary boronic acid a Miyaura borylation was put in place using Pd(Cl)2(ddpf) and bis(pinacolato)diboron which provided pinacol ester 11, in 95% yield after silica gel chromatography. In 2007, Hayashi and coworkers disclosed an iridium-catalyzed [3+2] annulation of dienes with ortho-carboxylated phenylboronic acids. We decided to apply this methodology for the first time to the total synthesis of a natural product. Initial attempts to use the boronic acid 7 as the substrate in this cyclization provided at the most indole 6 in 36% yield, and we decided to explore the in situ generation of boronic acid 7 via hydrolysis of pinacol ester 11 in the reaction medium. When we kept the reaction mixture in the dark, this one-pot approach proceeded regio- and stereoselectively to provide racemic linear tricyclic indole cis-6, in 94% yield, as the key synthetic intermediate in our approach.

**Scheme 2. Iridium-catalyzed preparation of linear tricyclic indole (+/-)-6.**
HPLC (provided the corresponding
by using coworkers.
matic resolution (1:1) dioxane, 80 °C, rt, 2.5 h.

S,S (36% yield, r(a) t(f) transesterification
ation of benzylic alcohols
ation with methallyl
HO N (1.25 equiv), isoprene

0.1 equiv), NaOH (1.75 equiv), TsCl (1.10 equiv), DCM, rt, 2.5 h, 95%. (b) DIBAL-H (2.0 equiv), DCM, 4.5 h, 0 °C – rt, quant. (c) MnO₂ (18.0 equiv), DCM, rt, 5 h, quant. (d) Pd(Cl)(dpdf) (0.05 equiv), KOAc (3.0 equiv), B₃(pin) (1.2 equiv), dioxane, 80 °C, 16 h, 95%. (e) H₂O (10.0 equiv), THF:toluene (1:1). (f) [Ir(OH)(COD)] (0.05 equiv), Et₂N (1.25 equiv), isoprene (10.0 equiv), THF:toluene (1:1), 80 °C, 24 h, 94%.

In order to secure indole 6 in enantiomerically pure form, enzymatic resolution with lipase B from Candida antarctica (CALB-Novozym® 435) known to be very selective for hydrolysis and transesterification of secondary alcohols, particularly in the acetylation of benzyllic alcohols as reported by Ferraz and coworkers.

After some experimentation which involved screening some solvents and amount of CALB, we found that by using a toluene/MTBE mixture (8:2, V/V) and increasing the amount of CALB to a 2:1 mass ratio compared to the substrate, treatment of benzyllic alcohol (+/-)-6 with vinyl acetate provided the corresponding enantiomerically pure acetate (S,S)-12 (30% yield) and enantiomerically pure alcohol (R,R)-6 (36% yield, >99% enantiomeric purity as determined by chiral HPLC, see SI).

Scheme 3. Enzymatic resolution of benzyllic alcohol (+/-)-6.

Conditions: vinyl acetate (4.0 equiv), CALB (2:1 mass ratio), toluene/MTBE (8:2), 64 °C, 34 h, 30% of (S,S)-12 and 36% of (R,R)-6 ee>99%.

In order to complete our synthetic approach to raputindole A (1), it remained the introduction of the isobutenyl side chain and the incorporation of the southern indole moiety. The former was planned to be introduced via allylation of the benzyllic carbonation to be derived from (R,R)-6 with methallytrimethylsilane which required screening of different Bronsted and Lewis acids.

Bismuth tribromide emerged as the best choice as it provided the desired methally substituted indole in 69% yield, albeit in a 2:1 molar ratio (cis:trans isomers). In an attempt to improve the ratio of the trans isomer, the installation of the southern indole moiety previous to the reaction with methallytrimethylsilane was examined. Although the Heck reaction of 6 with tosylindole 9, prepared according to literature procedure, provided bisindole 17 in 48% yield, its subsequent reaction with methallytrimethylsilane promoted by bismuth tribromide provided a complex mixture of products.

Despite the poor stereoselectivity observed in the installation of the isobutenyl side chain, we moved forward with the 2:1 mixture of cis and trans-13a:13b and proceeded to the isomerization of the double bond to convert the exo double bond to the required isobutenyl side chain. Treatment with p-TsOH, in toluene at 80 °C, afforded a 2:1 mixture of 14a:14b in almost quantitative yield. With the northern and southern moieties secured, the cis/trans mixture of indoles 14a:14b was submitted to the conditions of the Heck reaction employed for 6 to provide a 2:1 cis/trans mixture of 16a:16b, in 71% yield. The removal of both tosyl groups which have served well for the assembly of the key precursor 14a:14b was a challenging undertaking. Initially, we attempted to use TBAF in THF, thiglycolic acid as well as LiOH in THF but we only observed product degradation. The use of KOH and CTAB in THF–H₂O under transfer phase catalysis made the deprotection possible, but an inseparable mixture of raputindole A (1) and its monotosyl derivative was obtained. Inspection of the ¹H-NMR spectrum of the crude mixture, revealed the formation of a multiplet at 6 6.5-6.53 ppm which correlates with the one observed in 6-iodo-indole 9 and is suggestive of the southern indole moiety. This conclusion was also corroborated by NOESY analysis of the crude mixture. After extensive experimentation, we found that NaOH in THF/MeOH at 64 °C was the best condition to remove both tosyl groups providing a mixture of raputindole A (1) and its C-6 epimer in 67% yield which was separated by preparative chiral HPLC (Chiralpak IA column) to afford raputindole A (1) spectroscopically identical to the natural product (see SI).
In summary, we have accomplished the diastereoselective total synthesis of (+)-raputindole A (1) through the stereoselective iridium-catalyzed cyclization and enzymatic resolution which allowed the obtention of the northern part of raputindole A (1), as a 2:1 mixture of cis/trans 13a/13b, after installation of the isobutenyl side chain at C-6. After merging it with 6-iodoindole 15 (southern part) via Heck reaction and removal of both tosyl groups, (+)-raputindole A (1) was isolated after preparative chiral HPLC separation in 10 steps (LLS) and 10% overall yield. The versatility of our proposal stems from the possibility to use a chiral version of the iridium catalyst to develop an asymmetric synthesis of raputindole A (1). Also, with minor adaptations our route is amenable to the total synthesis of other members of the raputindole family such as raputindole B (2) and deoxiraputindole C (4) as well as to derivatives thereof to support structure-activity relationship studies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and spectral data for all new compounds (PDF).

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Diastereoselective Total Synthesis of (+)-Raputindole A: An Iridium-catalyzed Cyclization Approach

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Supporting Information

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NMR Spectra ............................................................................................................................24
All the solvents were kept under a nitrogen atmosphere. Dimethylformamide (DMF) and TMEDA were distilled after 12 hours under 4 A molecular sieves. Tetrahydrofuran (THF) was distilled under sodium-benzophenone immediately prior to use.\textsuperscript{1} Dichloroethane (DCE), dichloromethane (DCM) and trimethylamine (Et\textsubscript{3}N) were distilled from calcium hydride under a nitrogen atmosphere prior to use. The other anhydrous solvents were used without further purification, unless otherwise specified. The commercial reagents were used without further purification, unless otherwise stated. Oven-dried syringes were used to transfer the anhydrous solvents. The progress of the reactions was monitored by thin chromatography (TLC) using 0.25 mm E. Merck silica plates 60-F254 or neutral alumina. The visualizing agents were UV light (254 nm), p-anisaldehyde, curcumin and/or phosphomolybdic acid stain solutions and heat as developing agents. The purifications of the crude reaction mixtures were carried out using flash silica gel chromatography (Merck, 40-63 µm) under positive pressure. NMR spectra were recorded on Bruker Alli 300 or 500 MHz, Varian Gemini 400 MHz and Bruker Alli 800 MHz equipped with with cryoprobe. Chemical shifts (δ) are in parts per million (ppm) and the calibration was performed with reference to residual non-deuterated solvent (CHCl\textsubscript{3} \textsuperscript{1}H RMN δ 7.26 ppm, \textsuperscript{13}C NMR 77.0 ppm). The following descriptors were used to describe the NMR data: chemical shift (ppm), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hertz) and integration. Infrared spectra were recorded on a Thermo Scientific iD3 spectrometer. High resolution mass spectra (HRMS) were recorded in a MicroToF Bruker Daltonics and in an Agilent Technologies 6530 Accurate-Mass Q-TOF LC-MS. The specific optical rotations were measured on a Perkin Elmer 341 polarimeter (sodium line = 589.3 nm).
Synthetic procedures

**Methyl 5-bromo-1-tosyl-1H-indole-6-carboxylate (8b)**

To a soln. of indole 8 (1.00 g, 3.94 mmol, 1.0 eq.) in DCM (150 mL) was added TEBAC (0.092 g, 0.39 mmol, 0.1 eq.). Then NaOH (0.276 g, 6.89 mmol, 1.75 eq.) and TsCl (0.826 g, 4.33 mmol, 1.1 eq.) were successively added. The reaction flask was stirred at room temperature for 5 hours. The reaction mixture was quenched with H$_2$O (50 mL) and 1 M hydrochloric acid (30 mL) and the resulting mixture was stirred for 10 min. The aqueous layer was separated and extracted with 3% methanol/chloroform soln. (3 x 100 mL). The combined organic layer was washed with brine, dried over MgSO$_4$ and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO$_2$, 10-20% AcOEt/hexanes) to provide 8b in 95% yield (1.53 g, 3.75 mmol) as a white solid.

$^1$H NMR (800 MHz, CDCl$_3$) δ 8.46 (s, 1 H); 7.81 (s, 1 H); 7.76 (d, J = 8.0 Hz; 2 H); 7.67 (d, J = 4.0 Hz; 1 H); 7.25 (d, J = 8.0 Hz; 2 H); 6.61 (dd, J = 0.8 and 3.2 Hz; 1 H); 3.98 (s, 3 H); 2.36 (s, 3 H).

$^{13}$C NMR (200 MHz, CDCl$_3$) δ 166.7; 145.6; 134.8; 134.3; 133.1; 130.2; 130.0; 127.6; 126.8; 126.7; 116.6; 115.6; 108.0; 52.7; 21.6.

IR (cm$^{-1}$) 1727; 1593; 1452; 1425; 1403; 1374; 1279; 1222; 1169; 1101; 1010; 982; 930; 889; 864; 815; 768; 727; 708.

HRMS (ESI-TOF) m/z [M+H$^+$]: calcd for C$_{17}$H$_{15}$NO$_4$SBr = 407.9905 Da, found = 407.9887 Da (error = 4.4 ppm).

**Mp:** 155.0-155.8 °C.

(5-Bromo-1-tosyl-1H-indol-6-yl)metanol (9)
To a flame dried Schlenk flask was added 8b (0.520 g, 1.27 mmol, 1.0 equiv) and DCM (10 mL). The soln. was cooled to 0 °C and then DIBALH (1M in toluene, 2.54 mL, 2.54 mmol, 2.0 equiv) was slowly added. The reaction mixture was stirred for 1 hour and the temperature was let to reach room temperature. After 3 hours, the reaction was completed by TLC and the reaction temperature was decreased to 0 °C. AcOEt (8 mL) was slowly added, followed by the addition of Rochelle’s salt soln. (1M soln., 8 mL, 8 mmol) and Et₂O (40 mL). The reaction mixture was stirred overnight and then the aqueous layer was separated and extracted with 3% MeOH in chloroform soln. (3 x 15 mL). The combined organic layer was washed with brine, dried (MgSO₄) and the solvent was removed under reduced pressure. The product 9 was obtained in quantitative yield (0.484 g, 1.27 mmol).

**1H NMR (300MHz, CDCl₃)** δ 8.10 (s, 1H); 7.77 (s, 1H); 7.73 (d, J = 9.0 Hz, 2H), 7.57 (d, J = 6.0 Hz, 1H); 7.24 (d, J = 9.0 Hz, 2H); 6.59 (dd, J = 0.3 and 3.6 Hz, 1H); 4.83 (s, 2H); 2.35 (s, 3H).

**13C NMR (126 MHz, d6-(CD₃)₂CO):** δ 146.3, 138.0, 135.7, 135.0, 131.8, 130.7, 128.4, 127.5, 125.2, 116.7, 113.4, 108.9, 64.3, 21.2.

**HRMS (ESI-TOF) m/z [M-H₂O]⁺:** calcd for C₁₆H₁₁NO₂SBr = 361.9850 Da, found= 361.9863 Da (error = 3.59 ppm).

**Mp:** 136.7 – 139.2 °C.

**IR (cm⁻¹):** 1411; 1367; 1164; 1123; 1057; 812; 688.

5-Bromo-1-tosyl-1H-indole-6-carbaldehyde (10)
In a round bottom flask was added a solution of 9 (1.164 g, 3.060 mmol, 1.0 equiv) in DCM (100 mL). MnO₂ (5.205 g, 55.10 mmol, 18 equiv) was then added and the mixture was stirred for at rt 5 h. The suspension was filtered in a Celite pad and washed with AcOEt (400 mL). After evaporation under reduced pressure, aldehyde 10 was obtained in quantitative yield (1.16 g, 3.06 mmol) as an off-white solid.

\[^{1}H\text{NMR (300MHz, CDCl}_3\text{): }\delta\text{ 10.42 (s, 1 H); 8.53 (s, 1 H); 7.82-7.76 (m, 4 H); 7.27 (m, 1 H); 7.25 (m, 1 H); 6.64-6.63 (dd, }J=0.87\text{ and 3.7 Hz; 1 H); 2.35 (s, 3 H).}\]

\[^{13}C\text{NMR (75 MHz, CDCl}_3\text{): }\delta\text{ 191.7, 145.7, 136.5, 134.6, 133.6, 131.3, 130.2, 129.2, 127.0, 125.9, 120.5, 115.1, 107.7, 21.6.}\]

\[\text{IR (cm}^{-1}\text{): 1686, 1598, 1417, 1276, 1167, 1090, 815, 765, 664.}\]

\[\text{Mp = 191.0 – 191.3°C}\]

\[\text{HRMS (ESI-TOF) m/z [M+H]^{+}: calcd for C}_{16}\text{H}_{13}\text{NO}_{3}\text{SBr = 377.9799 Da, found = 377.9779 Da (error = 5.3 ppm).}\]

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indole-6-carbaldehyde (11)

In a Schlenk flask charged with aldehyde 10 (1.014 g, 2.680 mmol, 1.0 equiv), bis(pinacolato)diboron (0.842 g, 3.22 mmol, 1.2 equiv), KOAc (0.790 g, 8.04 mmol, 3.0 eqv) and Pd(Cl)₂(dppf) (0.059 g, 0.080 mmol, 0.03 eqv) under nitrogen atmosphere was added degassed dioxane (36 mL). The reaction mixture was stirred at 80 °C for 16 hours. After this time, the reaction mixture was cooled to rt and the crude mixture was filtered in a Celite/SiO₂ pad and washed with AcOEt (300 mL). The solvent was removed under reduced pressure and
the crude product was purified by flash column chromatography (SiO₂, 10-20% AcOEt/hexanes) to provide 11 in 95% yield (1.085 g, 2.550 mmol) as an off-white thick oil.

**¹H NMR (400MHz, CDCl₃):**  δ 10.57 (s, 1 H); 8.56 (t, J = 0.8 and 1.2 Hz, 1 H); 8.02 (s, 1 H); 7.78 (d, J = 8.4 Hz; 2 H); 7.74 (d, J = 3.6 Hz; 1 H); 7.22 (d, J = 8.4 Hz, 2 H); 6.71 (dd, J = 1.2 and 3.6 Hz; 1 H); 2.32 (s, 3 H); 1.39 (s, 12 H).

**¹³C NMR (75 MHz, CDCl₃):**  δ 194.0, 145.4, 137.8, 135.7, 134.8, 134.4, 130.0, 130.0, 129.0, 126.8, 114.0, 108.9, 84.3, 25.0, 24.8, 21.5.

**IR (cm⁻¹):** 2978, 1680, 1477, 1455, 1414, 1373, 1331, 1279, 1169, 1120, 974, 853, 675.

(6-Formyl-1-tosyl-1H-indol-5-yl)boronic acid (7)

In a round bottom flask was added the aldehyde 11 (0.165 g, 0.389 mmol, 1.0 eq.) dissolved in acetone/H₂O (1:1, V/V, 8 mL). NaIO₄ (0.333 g, 1.56 mmol, 4.0 eq.) and NH₄OAc (0.150 g, 1.94 mmol, 5.0 eq.) were added and the reaction mixture was stirred 6 h at rt. The solvent was removed under reduced pressure and the product was extracted using a mixture of 5% MeOH/DCM (3 x 10 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and the solvent was reduced under reduced pressure to provide 7 in 96% yield as an orange solid (0.128 g, 0.373 mmol).

**¹H NMR (300 MHz, CDCl₃):**  δ 9.97 (s, 1H); 8.54 (s, 1H); 8.50 (s, 1H); 7.82 (m, 2H); 7.78 (s, 1H); 7.28 (m, 1H); 7.18 (s, 1H); 6.81 (m, 1H); 2.37 (s, 3H).

**¹³C NMR (75 MHz, d6-(CD₃)₂CO):**  δ 196.9, 147.6, 138.6, 136.4, 136.5, 136.3, 132.2, 131.9, 130.4, 128.7, 128.6, 120.3, 111.0, 22.2.

**HRMS (ESI-TOF) m/z [M-H₂O]⁺:**  calcd for C₁₆H₁₃BNO₅S = 326.0658 Da, found = 326.0655 Da (error = 0.92 ppm).

**Mp = 135-139 °C.**
(5R,7R) and (5S,7S)-5-Methyl-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[f]indol-7-ol (±/−-6)

A resealable pressurized tube equipped with a magnetic stir bar was charged with [Ir(Cl)(COD)]₂ (0.001 g, 0.001 mmol, 0.05 eq.) and degassed toluene (0.3 mL). Et₃N (0.005 mL, 0.036 mmol, 1.25 eq.) and isoprene (0.030 mL, 0.29 mmol, 10 eq.) were next added by a syringe. In another vessel, a solution of aldehyde 7 (0.010 g, 0.029 mmol, 1.0 eq.) in THF/toluene (0.7 mL, 5:2 V/V) which was cannulated to the resealable tube and the reaction mixture was protected from visible light and the temperature was increased to 55 °C. After 3 h (monitored by ¹H NMR) the reaction mixture was allowed to cool to rt and it was concentrated under reduced pressure. The resulting brown mixture was purified by flash column chromatography (SiO₂, 10-20% EtOAc/hexanes) to provide indole (±/−)-6 in 36% yield (0.0039 g, 0.011 mmol) as a yellow solid.

¹H NMR (300 MHz, CDCl₃): δ 8.01 (m, 1H), 7.81 (m, 2H), 7.57 (d, J = 6.0 Hz, 1H), 7.24 (m, 2H), 7.22 (m, 1H), 6.61 (dd, J = 1.5 and 6.0 Hz, 1H), 6.17 (m, 1H), 5.33 (m, 1H), 5.04 (m, 2H), 2.43 (m, 1H), 2.34 (s, 3H), 2.15 (m, 1H), 1.61 (brs, 1H), 1.32 (m, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 147.5, 144.9, 144.7, 141.7, 137.2, 134.5, 134.5, 131.7, 129.9, 126.9, 126.8, 116.1, 111.7, 109.5, 108.8, 74.6, 51.0, 47.9, 26.3, 21.6.

HRMS (ESI-TOF) m/z[M+Na]⁺: calcd for C₂₁H₂₁NO₃SNa = 390.1134 Da, found: 390.1150 Da (error = 4.1 ppm).

Mp = 84.1 – 89.9 °C.

IV (cm⁻¹) = 2359, 2343, 1372, 1167, 1109, 703, 668.
A resealable pressure tube equipped with a magnetic stir bar was charged with \([\text{Ir(Cl)(COD)}]_2\) (0.012 g, 0.017 mmol, 0.05 eq.) and degassed toluene (0.7 mL). Et3N (0.060 mL, 0.42 mmol, 1.5 eq.) and isoprene (0.340 mL, 3.34 mmol, 10.0 eq.) were next added via syringe. In another vessel, a solution of boronic acid 7 (0.142 g, 0.334 mmol, 1.0 eq.) in THF/toluene (3.5 mL, 3:2 V/V) was prepared and cannulated to the resealable reaction tube. Degassed H2O (0.060 mL) was added. The reaction flask was protected from visible light and the reaction temperature was increased to 80 °C. After 24 hours (monitored by 1H NMR) the reaction mixture was allowed to cool to rt and concentrated under reduced pressure. The resulting brown mixture was purified by flash column chromatography (SiO2, 10-20% EtOAc/hexanes) to provide indole (+/-)-6 in 94% yield (0.116 g, 0.315 mmol) as a yellow solid.

**(5R,7R) and (5S,7S)-5-Methyl-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[f]indol-7-yl acetate ((+/-)-12)**

To a solution of indole (+/-)-6 (0.020 g, 0.054 mmol, 1.0 eq.) in acetic anhydride (1.0 mL) in a round-bottom flask was added Et3N (0.0080 mL, 0.054 mmol, 1.0 eq.). After 2.5 h of stirring, the mixture was diluted with diethyl ether (3 mL) and washed with saturated NaHCO3 (2 x 3 mL). The organic layer was dried over MgSO4 and the solvent was removed under reduced pressure to provide (+/-)-12 as a yellow oil.4

**1H NMR (500 MHz, CDCl3):** δ 7.97 (s, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 3.5 Hz, 1H), 7.27 (m, 3H), 6.62 (dd, J = 0.5, 3.5 Hz, 1H), 6.31 (m, 1H), 6.12 (m, 1H), 5.08 (m, 2H), 2.50 (m, 1H), 2.37 (s, 3H), 2.24 (s, 1H), 2.13 (s, 3H) 1.38 (s, 3H).

**13C NMR (126 MHz, CDCl3) δ (ppm) =** 166.38, 146.2, 145.8, 144.9, 137.3, 135.3, 134.3, 132.2, 129.9, 127.1, 127.0, 115.9, 111.2, 110.4, 108.7, 76.4, 48.1, 47.5, 26.3, 22.2, 21.4.

**(5R,7R)-5-Methyl-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[f]indol-7-ol ((R,R)-6) and**
(5S,7S)-5-methyl-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[f]indol-7-yl acetate ((S,S)-12)

![Chemical structure of (S,S)-12 and (R,R)-6]

\[
\text{HO} \quad \text{Ts} \quad \text{Ts} \quad \text{AcO} \quad \text{HO} \\
\text{(S,S)-12 (30%)} \quad + \quad \text{(R,R)-6 (36%)}
\]

Table 1. Optimization of enzymatic resolution

| Entry | Solvent                  | CALB (equiv) | Time (h) | Conversion | e.e.   |
|-------|--------------------------|--------------|----------|------------|--------|
| 1     | Toluene                  | 1.2          | 17       | 25         | >99%   |
| 2     | Toluene:MTBE (4:1)       | 1.2          | 17       | 37.5       | >99%   |
| 3     | Toluene:MTBE (4:1)       | 1.2          | 34       | 47.5       | >99%   |
| 4     | Toluene:MTBE (4:1)       | 2.0          | 17       | 40         | >99%   |
| 5     | Toluene:MTBE (4:1)       | 2.0          | 34       | 50         | >99%   |
| 6     | Toluene:MTBE (4:1)       | 2.0          | 34       | 50 (30/36) | >99%   |

\(^a\) yields of \((S,S)-12/(R,R)-6\).

To a magnetically stirred solution of alcohol \((+/−)-6\) (0.080 g, 0.22 mmol, 1.0 eq.) in a toluene/MTBE mixture (6.40 mL, 8:2 V/V) was added CALB (0.160 g, 2.0 g/g alcohol). The reaction mixture was warmed to 64 °C and after 15 minutes, vinyl acetate (0.080 mL, 0.87 mmol, 4.0 eq.) was added. After 34 h, the reaction mixture was allowed to cool to rt. The solids were filtered off and washed with EtOAc (40 mL) and DCM (40 mL). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (SiO\(_2\), 5-30\% EtOAc/hexanes). The enantiomerically pure acetylated product \((S,S)-12\) was isolated in 30\% yield (0.0264 g, 0.064 mmol) as a colorless thick oil and the enantiomerically pure alcohol \((R,R)-6\), in 36\% yield (0.029 g, 0.078 mmol) as a viscous oil. The enantiomeric excess (ee) of 99\% was determined by HPLC using an analytical column Chiralpak IA.

(5R,7R)-5-Methyl-7-(2-methylallyl)-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[f]indole (13a) and (5R,7S)-5-Methyl-7-(2-methylallyl)-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[f]indole (13b)
To a resealable pressure tube charged with BiBr₃ (0.031 g, 0.069 mmol, 0.2 eq.) under nitrogen atmosphere was added a solution of indole \((R,R)-6\) (0.127 g, 0.345 mmol, 1.0 eq.) and methallylsilane\(^3\) (0.12 mL, 0.69 mmol, 2.0 eq.) in DCE (1.7 mL). After 1 hour under stirring at room temperature the reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography (SiO₂, 5% EtOAc/hexanes) to provide a 2:1 mixture of \(13a\) and \(13b\) in 69% yield (0.096 g, 0.24 mmol) as a colorless viscous oil.

\(^1\)H NMR (\(13b\) and \(13a\)): 6 7.82 (s, 1 H), 7.78 (d, \(J = 8.5\) Hz, 2 H), 7.50 (m, 1 H), 7.24 (m, 3 H), [6.57, m (major) and 6.59, m (minor), 1H], [6.05, m (major) and 5.97 m (minor), 1H], 5.11 (m, 2H), 4.88 (m, 2 H), [3.50 m (major) and 3.38 m (minor), 1H], 2.70 (dd, \(J = 6.0\) and 14.5 Hz, 1H), 2.35 (s, 3 H), 2.32 (m, 1H), 2.19 (m, 2H), 1.87 (s, 3 H), 1.28 (s, 3 H).

\(^13\)C NMR 147.1, 146.2, 146.2, 144.7, 144.3; 143.7, 135.5, 134.4, 129.8, 126.9, 125.9, 115.6, 111.8, 111.6, 108.9, 108.6, 48.4, 47.6, 43.9, 39.7, 25.7, 22.5, 21.5.

HRMS (ESI-TOF) \(m/z[M+H]^+\): calcd for \(C_{23}H_{28}NO_2S = 406.1841\) Da, found = 406.1822 Da (error = 4.7 ppm).

\(IV\) (\(cm^{-1}\)): 2964, 2914, 2857, 1634, 1595, 1494, 1441, 1370, 1340, 1285, 1230, 1183, 1167, 1120, 1092, 999, 919, 878, 806, 732, 702, 672

\((5R,7S)-5\)-methyl-7-(2-methylprop-1-en-1-yl)-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[f]indole (14a)

\((5R,7R)-5\)-methyl-7-(2-methylprop-1-en-1-yl)-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[f]indole (14b)
To a 2:1 mixture of indoles 13a and 13b (0.096 g, 0.24 mmol, 1.0 eq.) in a resealable pressure tube was added dry toluene (8 mL). Then TsOH (0.050 g, 0.28 mmol, 1.2 eq.) was added and the temperature was increased to 80 °C. The reaction progress was accompanied by $^1$H NMR and after 4 h, the reaction mixture was cooled to rt and concentrated under reduced pressure. The crude product was treated with satd. aq. NaHCO$_3$ soln. (10 mL) and extracted with EtOAc (3 x 15 mL). The mixture of products 14a and 14b was obtained as a brown viscous oil in 98% yield (0.094 g, 0.23 mmol) and used in the next step without purification.

$^1$H NMR (14b and 14a): $\delta$ 7.75 (m, 3H), 7.60 (s, 1H), 7.48 (d, $J$ = 4.0 Hz, 1H), 7.22 (m, 2H), 7.14 (s, 1H), [6.59 m (minor) and 6.56 m (major), 1H], [6.05 m (major) and 6.00 m (minor), 1H], 5.17 (m, 1H), 5.11 (m, 1H), 4.15 m (major) and 4.02 m (minor), 1H), 2.35 (s, 3H), 2.16 (m, 1H), 1.86 (m, 1H), 1.86 (s, 6H), 1.30 (s, 3H).

$^{13}$C NMR (500 MHz) = 146.6, 146.1, 144.7, 143.6, 135.4, 134.4, 133.1, 130.1, 129.7, 127.7, 127.0, 125.8, 115.4, 111.7, 109.3, 108.9, 48.9, 48.7, 41.5, 25.9, 24.9, 21.5, 18.3.

IV (cm$^{-1}$): 2961, 2923, 2860, 1639, 1598, 1458, 1439, 1367, 1342, 1290, 1238, 1189, 1169, 1114, 1032, 996, 908, 883, 883, 809, 760, 732, 699, 669.

**6-iodo-1-tosil-1H-indol (15)**

To a solution of indole 19 (0.854 g, 3.51 mmol, 1.00 eq.) in DCM (35 mL) was added TEBAC (0.080 g, 0.35 mmol, 0.10 eq.). Then, NaOH (0.203 g, 6.15 mmol, 1.75 eq.) and TsCl (0.734 g, 3.864 mmol, 1.10 eq.) were added. The reaction mixture was stirred at room temperature for
16 h and quenched with H$_2$O (50 mL) and of 1 M HCl (30 mL). After stirring for 10 min, the aqueous layer was separated and extracted with DCM (3 x 100 mL). The organic layer was washed with brine, dried over MgSO$_4$ and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO$_2$, 5-10% AcOEt/hexanes) to provide 15 (1.14 g, 2.86 mmol) in 81% yield as a yellow solid.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.36 (t, $J$ = 6.6 Hz, 1 H), 7.75 (d, $J$ = 8.4 Hz, 2 H), 7.52 – 7.47 (m, 2 H), 7.27 – 7.22 (m, 3 H), 6.61 (dd, $J$ = 3.9 and 0.9 Hz, 1 H), 2.34 (s, 3 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 145.2, 135.7, 135.0, 132.2, 130.0, 129.9, 126.7, 126.5, 122.8, 122.3, 108.7, 88.7, 21.5.

HRMS (ESI-TOF) m/z[M+H]$^+$: calcd for C$_{15}$H$_{13}$INO$_2$S = 397.9707 Da, found = 397.9708 Da.

Mp = 124.8 - 125.3 °C.

$(5R,7R)$-5-Methyl-1-tosyl-5-((E)-2-(1-tosyl-1H-indol-6-yl)vinyl)-1,5,6,7-tetrahydrocyclopenta[f]indol-7-ol (17)

To a dried round bottom flask charged with the tricyclic indole (+/-)-6 (0.030 g, 0.081 mmol, 1.00 eq.), 6-iodo-indole 14 (0.065 g, 0.16 mmol; 2.0 eq.), NaOAc (0.013 g, 0.16 mmol, 2.0 eq.), Pd(OAc)$_2$ (0.002 g, 0.008 mmol, 0.1 eq.) and n-Bu$_4$NBr (0.0060 g, 0.016 mmol, 0.20 eq.). Degassed DMAA/H$_2$O (0.96 mL, 9:1, V/V) was added under a nitrogen atmosphere and the reaction mixture was kept under stirring at 100 °C for 12 h. After that, the reaction mixture was allowed to reach rt and quenched by the addition of H$_2$O (2 mL), extracted with DCM (3 x 5 mL), washed with saturated solution of NaHCO$_3$ (30 mL) and brine (40 mL). The combined organics were dried over MgSO$_4$, filtered and the solvent was removed by reduced pressure. The crude product was purified by flash column chromatography (SiO$_2$, 5-10% AcOEt/hexanes) to furnish tosyl indole 17 (0.025 g, 0.039 mmol) in 48% yield as a yellow oil.
$^1$H NMR (500 MHz, CDCl$_3$): δ 8.05 (m, 1H), 7.91 (m, 1H), 7.82 (m, 2H), 7.73 (m, 2H), 7.59 (d, J = 3.5 Hz, 1H), 7.49 (d, J = 4.0 Hz, 1H), 7.41 (m, 1H), 7.32 (s, 1H), 7.29 (dd, J = 1.5 and 8.0 Hz, 1H), 7.25 (m, 2H), 7.21 (m, 2H), 6.63 (dd, J = 0.8 and 3.6 Hz, 1H), 6.59 (dd, J = 0.65 and 3.65 Hz, 1H), 6.56 (d, J = 16.1 Hz, 1H), 6.49 (d, J = 16.1 Hz, 1H), 5.38 (t, J = 6.2 Hz, 1H), 2.55 (m, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 2.26 (m, 1H), 1.47 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 144.9, 144.9, 141.7, 139.0, 135.4, 135.4, 134.6, 134.2, 131.8, 130.0, 127.4, 126.9, 126.7, 126.6, 121.4, 121.3, 116.3, 111.7, 109.5, 109.1, 108.8, 75.0, 74.5, 51.7, 47.5, 27.0, 24.8, 21.6, 21.5.

HRMS (ESI-TOF) m/z[M+H-H$_2$O]+: calcd for C$_{36}$H$_{31}$N$_2$O$_5$S$_2$ = 619.1720 Da; found = 619.1710 Da (error = 1.8 ppm).

(5R,7S)-5-methyl-7-(2-methylprop-1-en-1-yl)-1-tosyl-5-((E)-2-(1-tosyl-1H-indol-6-yl)vinyl)-1,5,6,7-tetrahydrocyclopenta[f]indole (16a) and (5R,7R)-5-methyl-7-(2-methylprop-1-en-1-yl)-1-tosyl-5-((E)-2-(1-tosyl-1H-indol-6-yl)vinyl)-1,5,6,7-tetrahydrocyclopenta[f]indole (16b)

To a dried round bottom flask charged with a 2:1 mixture of tricyclic indoles 14a and 14b (0.0080 g, 0.020 mmol, 1.0 eq.), iodoindole 15 (0.016 g, 0.039 mmol; 2.0 eq.), NaOAc (0.0030 g, 0.039 mmol, 2.0 eq.), Pd(OAc)$_2$ (0.044 g, 0.0020 mmol, 0.10 eq.) and n-Bu$_4$NBr (0.001 g, 0.004 mmol, 0.2 eq.) was added degassed DMAA/H$_2$O (0.5 mL, 9:1, V/V) under nitrogen atmosphere and the reaction mixture was kept under stirring at 100 °C for 22 h. The reaction mixture was stirred at 100 °C for 12 h, allowed to reach rt and quenched with H$_2$O (1 mL) extracted with DCM (3 x 5 mL), washed with saturated solution of NaHCO$_3$ (15 mL) and brine (20 mL), dried over MgSO$_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO$_2$, 5-10% AcOEt/hexanes) to furnish a mixture of diastereomers 16a:16b (0.0094 g, 0.014 mmol), in 71% yield, as a yellow solid.
The diastereoisomers were separated by preparative HPLC using a chiral column Chiralpak® IA (21 x 250 mm, 5 µm, 3:97 V/V, i-PrOH/hexanes, isocratic mode, flow 12.6 mL/min, UV detection at 291 nm).

**Minor isomer (16b)**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.83 (s, 1H), 7.79 (d, $J = 8.4$ Hz, 2H), 7.72 (d, $J = 8.4$ Hz, 2H), 7.65 (s, 1H), 7.54 (d, $J = 3.6$ Hz, 1H), 7.47 (d, $J = 3.6$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 7.31 (s, 1H), 7.23 (m, 5H), 6.64 (dd, $J = 0.8$ and 3.6 Hz, 1H), 6.57 (dd, $J = 0.8$ and 3.6 Hz, 1H), 6.43 (d, $J = 16.0$ Hz, 1H), 6.10 (d, $J = 16.0$ Hz, 1H), 5.18 (m, 1H), 4.09 (m, 1H), 2.47 (m, 1H), 2.35 (d, $J = 10.4$ Hz, 6H), 1.88 (s, 3H), 1.84 (s, 3H), 1.84 (m, 1H), 1.25 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 144.9, 144.8, 144.7, 144.4, 138.1, 135.4, 135.4, 135.4, 135.4, 134.5, 133.4, 131.3, 129.9, 129.8, 129.7, 127.7, 127.0, 126.7, 126.0, 126.4, 125.8, 121.5, 121.1, 115.8, 111.5, 109.2, 109.1, 109.0, 49.6, 48.5, 41.2, 26.9, 25.9, 21.6, 21.5, 18.4.

IV (cm$^{-1}$): 3896, 3849, 3838, 3747, 3742, 3497, 3494, 3472, 1450, 1433, 1367, 1169, 1117, 1090, 996, 881, 809, 732, 696.6.

HRMS (ESI-TOF) $m/z$[M+H]$^+$ of 15a and 15b:: calcd for C$_{40}$H$_{39}$N$_2$O$_4$S$_2$ = 675.2351 Da, found = 675.2313 Da (Error = 5.6 ppm)

Mp: 106.7-109.1 °C.

**Major isomer (16a)**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.96 (s, 1H), 7.76 (m, 4H), 7.65 (s, 1H), 7.50 (m, 2H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.34 (dd, $J = 1.6$, 8.4 Hz, 1H), 7.22 (m, 5H), 6.65 (d, $J = 16.0$, 1H), 6.60 (dd, $J = 0.8$, 3.6 Hz, 1H), 6.56 (dd, $J = 0.8$, 3.6 Hz, 1H), 6.49 (d, $J = 16$, 1H), 5.22 (m, 1H), 4.23 (m, 1H), 2.36 (d, $J = 9.6$ Hz, 6H), 2.30 (m, 1H), 2.00 (m, 1H), 1.89 (d, $J = 1.2$ Hz, 6H), 1.45 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 146.2, 144.9, 144.8, 143.6, 143.5, 138.6, 135.4, 135.4, 134.6, 134.5, 133.3, 130.2, 129.9, 129.9, 127.6, 127.4, 127.0, 126.7, 126.5, 125.9, 121.4, 121.3, 114.4, 115.6, 111.6, 109.4, 109.1, 108.9, 49.4, 48.5, 41.6, 25.9, 25.6, 21.6, 21.5, 18.4.

HRMS (ESI-TOF) $m/z$[M+H]$^+$ of 15a and 15b: calcd for C$_{40}$H$_{39}$N$_2$O$_4$S$_2$ = 675.2351 Da, found = 675.2313 Da (error = 5.6 ppm).
**Mp:** 104.2-109.2 °C.

**IV (cm⁻¹):** 3846, 3830, 3813, 3791, 1436, 1373, 1271, 1172, 1114, 1092, 1026, 1002, 966, 848, 812, 719, 699.

(5R,7R)-5-((E)-2-(1H-Indol-6-yl)vinyl)-5-methyl-7-(2-methylprop-1-en-1-yl)-1,5,6,7-tetrahydrocyclopenta[f]indole (1)

To a solution of bisindole 16a:16b (0.055 g, 0.11 mmol, 1.0 eq.) dissolved in a mixture of MeOH/THF (1.2 mL, 2:1, V/V) was added NaOH (0.036 g, 0.81 mmol, 10 eq.). The reaction mixture was warmed to 64 °C and stirred during 12 h. Upon completion of the reaction, the organic solvent was removed under reduced pressure and H₂O was added (1 mL). The mixture was extracted with EtOAc (3 x 3 mL) and the combined organic layer was washed with brine. After drying over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by column chromatography (activated neutral alumina, 5-20% EtOAc/hexanes) to provide raputindole A (1), as the minor isomer, together with its C-6 epimer (1:2 ratio), in 67% yield (0.020 g, 0.055 mmol) as a yellow oil. The diastereoisomers were separated by preparative HPLC using a chiral column Chiralpak® IA (21 x 250 mm, 5 µm, 12:88 V/V, i-PrOH/hexane, isocratic mode, flow 12.6 mL/min, UV detection at 291 nm). Pure (+)-raputindole A (1) ([α]²₀ = +76 (c 0.10, MeOH, 20 °C)) was isolated (Rₜ = 32.11 min) and its C-6 epimer (Rₜ = 36.73 min) both as colorless oil.

(+) Raputindole A (1)
$^1$H NMR (500 MHz, CDCl$_3$) δ (ppm) = 8.04 (br s, 1H, H-1’), 8.02 (br s, 1H, H-1”), 7.50 (d, J = 8.25, 1H, H-4”), 7.44 (s, 1H, H-4’), 7.26 (s, 1H, H-7”), 7.17 (t, J=2.45, 1H, H-2’), 7.15 (m, 1H, H-5”), 7.13 (m, 1H, H-2”), 7.08 (s, 1H, H-7’), 6.53 (m, 1H, H-3’), 6.47 (m, 1H, H-3”), 6.45 (d, J = 15.9, 1H, H-2), 6.15 (d, J = 16.9, 1H, H-1), 5.22 (d, J = 9.0, 1H, H-7), 4.07 (m, 1H, H-6), 2.44 (dd, J = 6.85 and 12.1, 1H, H-5β), 1.82 (m, 1H, H-5α), 1.82 (d, 3H, J = 1.4, H-9), 1.79 (d, 3H, J = 1.3, H-10), 1.61 (s, 3H, H-4).

$^{13}$C NMR (800 MHz, CDCl$_3$) δ (ppm) = 142.2 (C-6’), 141.5 (C-5’), 137.2 (C-2), 136.2 (C-7”a), 135.7 (C-7’a), 132.6 (C-8), 132.2 (C-6”), 128.3 (C-7), 127.2 (C-3’a), 127.0 (C-3”a), 126.8 (C-1), 124.3 (C-2”), 123.7 (C-2’), 120.5 (C-4”), 118.5 (C-5”), 115.0 (C-4’), 108.9 (C-7”), 106.2 (C-7’), 102.6 (C-3”), 102.5 (C-3’), 49.9 (C-5), 48.4 (C-3), 41.0 (C-6), 27.2 (C-4), 25.9 (C-9), 18.3 (C-10).

HRMS (ESI-TOF) m/z [M+H$^+$]: calcd for C$_{26}$H$_{27}$N$_2$ = 367.2174 Da, found = 367.2166 Da (Error = 2.2 ppm).

[α]$^{22}_D$ = +76 (c 0.10, MeOH, 20 °C)

**Figure 3.** HPLC chromatogram of mixture (+)-raputindole A and *epi*-raputindole A. Chiral column Chiralpak® IA (4.6 x 250 mm, 5 µm, 12:88 V/V, i-PrOH/hexane, isocratic mode, flow 0.6 mL/min, UV detection at 291 nm).
Figure 4. Differences δ (ppm) between $^1$H NMR (+)-raputindole A (1) synthetic and natural.

Figure 5. Numbering of Hydrogens.

Table 2. Comparative between $^1$H NMR chemical shifts of synthetic and natural (+)-raputindole A (1), in ppm.

| Hydrogen | Natural | JR670 | (Nat – JR670) |
|----------|---------|-------|---------------|
| H4       | 1,61    | 1,61  | 0             |
| H10      | 1,79    | 1,79  | 0             |
| H9       | 1,82    | 1,82  | 0             |
| H5a      | 1,82    | 1,82  | 0             |
| H5b      | 2,45    | 2,44  | 0,01          |
Figure 5. Differences $\delta$ (ppm) between $^{13}$C NMR (+)-raputindole A (1) synthetic and natural.
Table 3. Comparative between $^{13}$C NMR chemical shifts of (+)-raputindole A (1) synthetic and natural in ppm.

| Carbon | Natural | JR670 | (Nat – JR670) |
|--------|---------|-------|---------------|
| C10    | 18,3    | 18,3  | 0             |
| C9     | 25,9    | 25,9  | 0             |
| C4     | 27,20   | 27,1  | 0,1           |
| C6     | 41      | 41    | 0             |
| C3     | 48,4    | 48,4  | 0             |
| C5     | 50      | 50    | 0             |
| C3'    | 102,6   | 102,5 | 0             |
| C3''   | 102,7   | 102,6 | 0,1           |
| C7'    | 106,2   | 106,2 | 0             |
| C7''   | 108,9   | 108,9 | 0             |
| C4'    | 115     | 115   | 0             |
| C5''   | 118,5   | 118,5 | 0             |
| C4''   | 120,5   | 120,5 | 0             |
| C2'    | 123,7   | 123,7 | 0             |
| C2''   | 124,2   | 124,3 | -0,1          |
| C1     | 126,9   | 126,8 | 0,1           |
| C3''a  | 127,1   | 127   | 0,1           |
| C3'a   | 127,2   | 127,2 | 0             |
| C7     | 128,4   | 128,3 | 0,1           |
| C6''   | 132,3   | 132,2 | 0,1           |
| C8     | 132,6   | 132,6 | 0             |
| C7'a   | 135,8   | 135,7 | 0,1           |
| C7''a  | 136,3   | 136,2 | 0,1           |
| C2     | 137,2   | 137,2 | 0             |
| C5'    | 141,6   | 141,5 | 0,1           |
| C6'    | 142,2   | 142,2 | 0             |
6-epi-Raputindole A (6-epi-1)

\[^1\text{H NMR (500 MHz, CDCl}_3\text{)} \delta (\text{ppm}) = 8.10 (\text{brs, 1H}), 8.02 (\text{brs, 1H}), 7.56 (d, J = 8.25 \text{ Hz, 1H}), 7.43 (s, 1H), 7.36 (s, 1H), 7.17 (dd, J = 2.3, 3.1, 3.3 \text{ Hz, 1H}), 7.13 (dd, J = 2.45, 3.25, 3.15 \text{ Hz, 1H}), 7.08 (s, 1H), 6.67 (d, J = 16.05 \text{ Hz, 1H}), 6.53 (d, J = 16.05 \text{ Hz, 1H}), 6.51 (m, 1H), 6.45 (m, 1H), 5.25 (d, J = 9.0 \text{ Hz, 1H}), 4.22 (m, 1H), 2.26 (dd, J = 6.95, 12.25 \text{ Hz, 1H}), 2.00 (dd, J = 10.3, 12.35 \text{ Hz, 1H}), 1.85 (d, J = 1.35 \text{ Hz, 3H}), 1.83 (d, J = 1.4 \text{ Hz, 3H}), 1.49 (s, 3H).\]

\[^{13}\text{C NMR (800 MHz, CDCl}_3\text{)} \delta (\text{ppm}) = 143.27, 140.94, 137.81, 136.23, 135.61, 132.53, 132.28, 128.24, 127.38, 127.24, 127.10, 124.39, 123.86, 120.62, 118.56, 114.95, 108.72, 106.34, 102.64, 102.43, 49.78, 48.30, 41.34, 25.95, 25.57, 18.29.\]

\(\text{HRMS (ESI-TOF) m/z [M+H]^+]: \text{calcd for } C_{26}H_{27}N_2 = 367.2174 \text{ Da, found } = 367.2166 \text{ Da.}\)
Figure 1. HPLC chromatogram of racemic acetate 6c. Chiral column Chiralpak® IA (4.6 x 250 mm, 5 µm, 10:90 V/V, i-PrOH/hexane, isocratic mode, flow 1.0 mL/min, UV detection at 254 nm).

Figure 2. HPLC chromatogram of acetate 6a. Chiral column Chiralpak® IA (4.6 x 250 mm, 5 µm, 10:90 V/V, i-PrOH/hexane, isocratic mode, flow 1.0 mL/min, UV detection at 254 nm).
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NMR Spectra
$^1$H NMR (800 MHz, CDCl$_3$) Spectrum of Compound 8b. (residual water: in 1.55 ppm).

$^1$H NMR (800 MHz, CDCl$_3$) Spectrum of Compound 8b.
$^1$H NMR (800 MHz, CDCl$_3$) Spectrum of Compound 8b.

$^{13}$C NMR (200 MHz, CDCl$_3$) Spectrum of Compound 8b.
$^1$H NMR (300 MHz, CDCl$_3$) Spectrum of Compound 9. (residual water: 1.55 ppm).

$^1$H NMR (300 MHz, CDCl$_3$) Spectrum of Compound 9.
$^{13}$C NMR (126 MHz, $d_6$-(CD$_3$)$_2$CO) Spectrum of Compound 9.

$^1$H NMR (300 MHz, CDCl$_3$) Spectrum of Compound 10. (residual water: 1.59 ppm, residual hexanes grease: 1.25 and 0.88 ppm; residual silicon grease: 0.07 ppm).
$^1$H NMR (300 MHz, CDCl$_3$) Spectrum of Compound 10.

$^{13}$C NMR (75 MHz, CDCl$_3$) Spectrum of Compound 10. (residual hexanes grease: 29.7 ppm).
$^1$H NMR (400 MHz, CDCl$_3$) Spectrum of Compound 11. (dioxane: 3.70 ppm; residual hexanes grease: 1.27 ppm).

$^1$H NMR (400 MHz, CDCl$_3$) Spectrum of Compound 11.
$^{13}$C NMR (75 MHz, CDCl$_3$) Spectrum of Compound 11.

$^1$H NMR (300 MHz, CDCl$_3$) Spectrum of Compound (+/-)-6. (AcOEt: 4.12, 2.5 and 1.26 ppm).
$^1$H NMR (300 MHz, CDCl$_3$) Spectrum of Compound (+/-)-6.
$^1$H NMR (300 MHz, CDCl$_3$) Spectrum of Compound (+/-)-6.

$^{13}$C NMR (126 MHz, CDCl$_3$) Spectrum of Compound (+/-)-6.
$^1$H NMR (500 MHz, CDCl$_3$) Spectrum of Compound (+/-)-12.

$^3$H NMR (500 MHz, CDCl$_3$) Spectrum of Compound (+/-)-12.
$^1$H NMR (500 MHz, CDCl$_3$) Spectrum of a mixture 13a:13b cis/trans (2:1) of compounds 13a and 13b. (residual hexanes grease: 1.26 and 0.8 ppm; residual water: 1.55 ppm).
$^1$H NMR (500 MHz, CDCl$_3$) Spectrum of a mixture 13a:13b cis/trans (2:1).
$^1$H NMR (500 MHz, CDCl$_3$) Spectrum of a mixture 13a:13b cis/trans (2:1).

$^{13}$C NMR (126 MHz, CDCl$_3$) Spectrum of a mixture 13a:13b cis/trans (2:1).

$^1$H NMR (500 MHz, CDCl$_3$) Spectrum of a mixture 14a:14b cis/trans (2:1). (Obs.: spectrum with of 13a:13b).
$^1$H NMR (500 MHz, CDCl$_3$) Spectrum of a mixture 14a:14b cis/trans (2:1).

$^{13}$C NMR (126 MHz, CDCl$_3$) Spectrum of Compounds 14a:14b cis/trans (2:1).
DEPT135 (126 MHz, CDCl₃) Spectrum of Compounds mixture 14a:14b cis/trans (2:1).

³H NMR (300 MHz, CDCl₃) Spectrum of compound 15. (DCM: 5.27 ppm and TsCl impurity).
$^1$H NMR (300 MHz, CDCl$_3$) Spectrum of compound 15.

$^{13}$C NMR (75 MHz, CDCl$_3$) Spectrum of Compound 15.
$^1$H NMR (500 MHz, CDCl$_3$) Spectrum of compound 17.
$^1$H NMR (500 MHz, CDCl$_3$) Spectrum of compound 17.

$^1$H NMR (500 MHz, CDCl$_3$) Spectrum of compound 17.
$^{13}$C NMR (126 MHz, CDCl$_3$) Spectrum of Compound 17.

NOE 1D NMR (300 MHz, CDCl$_3$) Spectrum of compound 17. (irradiation: 5.38 ppm).
$^1$H NMR (400 MHz, CDCl$_3$) Spectrum of 16b. (residual hexanes grease: 1.26 and 0.8 ppm; residual water: 1.56 ppm).

$^1$H NMR (400 MHz, CDCl$_3$) Spectrum of 16b.
$^1$H NMR (400 MHz, CDCl$_3$) Spectrum of 16b.

$^{13}$C NMR (126 MHz, CDCl$_3$) Spectrum of Compound 16b.
$^1$H NMR (400 MHz, CDCl$_3$) Spectrum of 16a. (residual hexanes grease: 1.26 and 0.8 ppm; residual water: 1.56 ppm).

$^3$H NMR (400 MHz, CDCl$_3$) Spectrum of 16a.
$^1$H NMR (400 MHz, CDCl$_3$) Spectrum of 16a. (residual hexanes grease: 1.26 and 0.8 ppm; residual water: 1.56 ppm).

$^{13}$C NMR (126 MHz, CDCl$_3$) Spectrum of Compound 16a.
$^1$H NMR (500 MHz, CDCl$_3$) Spectrum of Raputindole A (1). (residual hexanes grease: 1.26 and 0.8 ppm; residual water: 1.56 ppm).
$^{13}$C NMR (200 MHz, CDCl$_3$) Spectrum of Raputindole A (1). (residual hexanes grease: 29.70 ppm).

COSY (500 MHz) of Raputindole A (1).
NOESY 2D (500 MHz) of Raputindole A (1).

HSQC (500 MHz) of Raputindole A (1).
HMBC (500 MHz) of Raputindole A (1).
