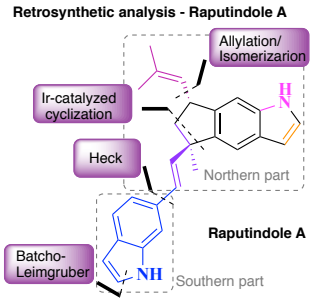
Diastereoselective Total Synthesis of (+)-Raputindole A: An Iridium-Catalyzed Cyclization Approach

Juliana L. L. F. Regueira[Ψ,†], Luiz F. Silva, Jr[Ψ,#], Ronaldo A. Pilli*[,†]

[Ψ]Institute of Chemistry, University of São Paulo (USP), CEP 05508-000 São Paulo, Brazil. [†]Institute of Chemistry, University of Campinas (UNICAMP), CEP 13083-970 Campinas, São Paulo, Brazil. [#]*In memorian*



ABSTRACT: This work describes the total synthesis of Raputindole A **(1)** through a convergent approach which features: 1) an iridium-catalyzed cyclization to assembly 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.[1] Other natural products containing this 1,2,3-unsubstituted pattern are trinkentrin A[3] and the herbindole family[4]. 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 D[5] 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-C[7] which can conceivably be traced back to the cyclization of two isoprenyl groups. Other examples of bisindole alkaloids include the spongotine A[8], caulindoles[9] and dragmacidin D[10] which, unlike raputindoles, have their indole moieties connected via C-3 (spongotine A and dragmacidin D) or via C-5 (caulindoles).[11] In fact, the raputindoles attracted the attention of the natural products practioners.[11]

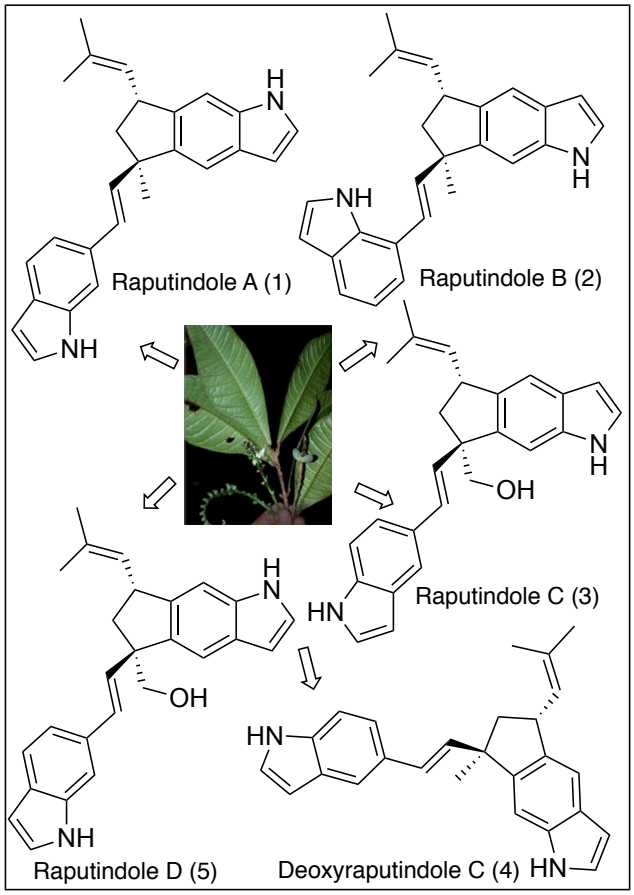


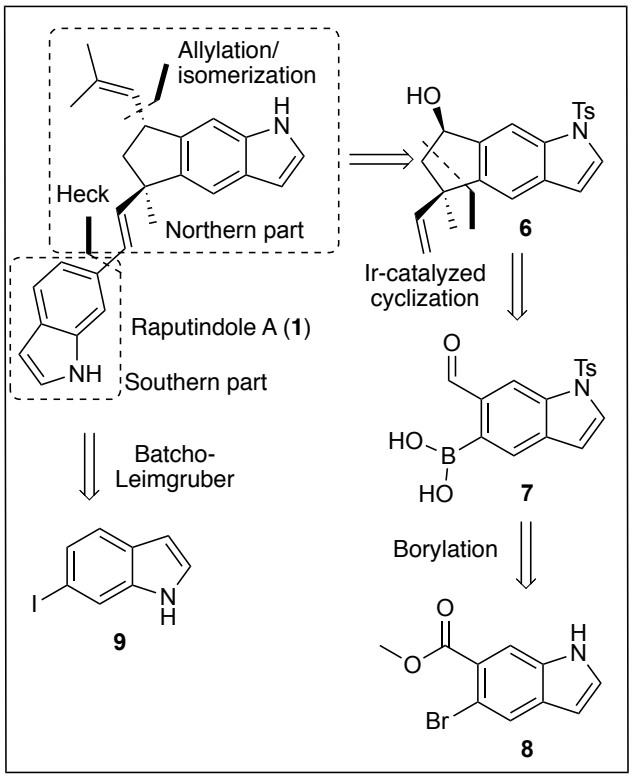
Figure 1. Members of the raputindole family. (Photo: Robin Foster, http://fieldmuseum.org/)

The absolute stereochemistry of raputindole A was determined in 2017 with the first total synthesis acomplished by Lindel and coworkers.[12] Their synthetitc 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**).[13] In addition to the Au(I)-catalyzed assembly of the cyclopentaindole 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 indoline 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[14] 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**).

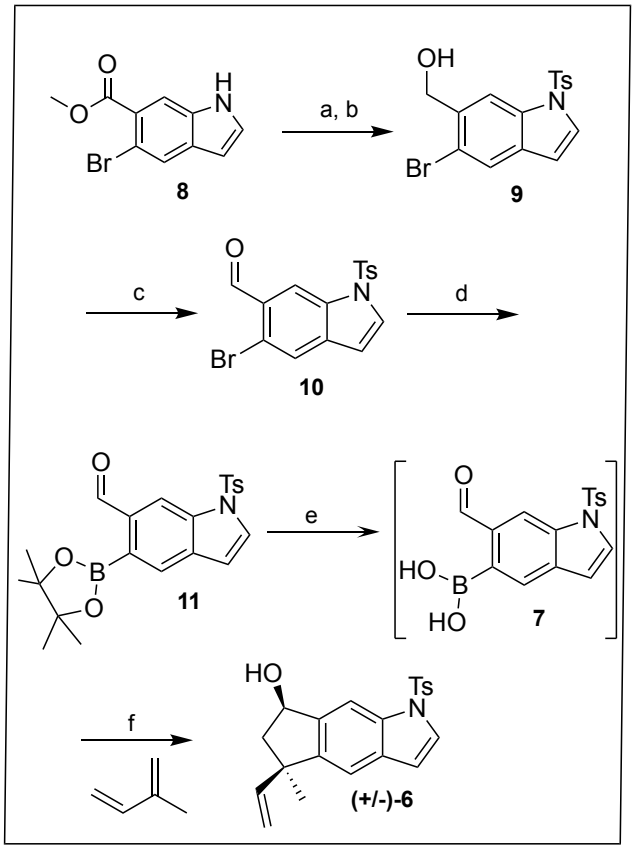
Our disconnection relies on a convergent approach where the northern and southern parts are connected via a Heck coupling reaction (scheme 1). The isobutenyl side chain would be installed by allylation of tricyclic alcohol **6** with allyltrimethylsilane.[15] The northern part would come from boronic acid **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.[14] 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(pinacolate)diboron which provided pinacol ester **11**, in 95% yield after silica gel chromatography.[16] In 2007, Hayashi and coworkers disclosed an iridium-catalyzed [3+2] annulation of dienes with *ortho*-carbonylated phenylboronic acids.[14] 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.[17]

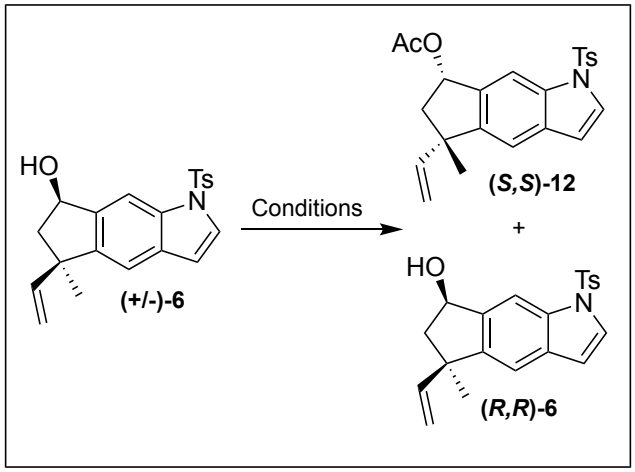
Scheme 2. Iridium-catalyzed preparation of linear tricyclic indole (+/-)-6.



(a) TEBAC (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) MnO_2 (18.0 equiv), DCM, rt, 5 h, quant. (d) $Pd(Cl)_2(dppf)$ (0.05 equiv), KOAc (3.0 equiv), $B_2(pin)_2$ (1.2 equiv), dioxane, 80 °C, 16 h, 95%. (e) H_2O (10.0 equiv), THF:toluene (1:1). (f) $[Ir(OH)(COD)]_2$ (0.05 equiv), Et_3N (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 benzylic alcohols as reported by Ferraz and coworkers.[18] 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 benzylic 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).[19,20]

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

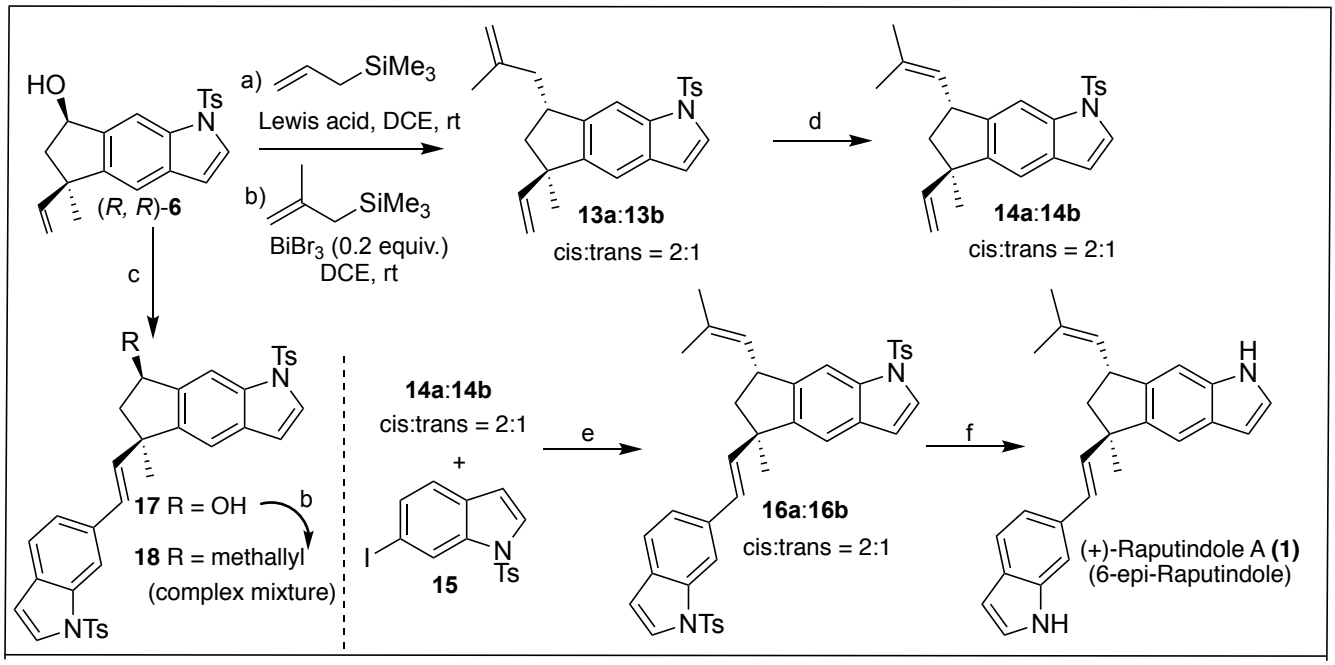


Conditions: vinyl acetate (4.0 equiv), CALB (2;1 mass ratio), toluene/MTBE (8:2), 64 °C, 34 h, 30% of **(*S*,*S*)-12** and 36% of **(*R*,*R*)-6** ee>99%.

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 benzylic carbocation to be derived from **(*R*,*R*)-6** with methallyltrimethylsilane which required screening of different Bronsted and Lewis acids.[21-23] Bismuth tribromide emerged as the best choice as it provided the desired methallyl 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 methallyltrimethylsilane was examined. Although the Heck reaction of **6** with tosylindole **9**, prepared according to literature procedure[24], provided bisindole 17 in 48% yield, its subsequent reaction with methallyltrimethylsilane 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.[25] 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, thioglycolic acid as well as LiOH in THF but we only observed product degradation. The use of KOH and CTAB in THF-H_2O under transfer phase catalysis made the deprotection possible, but an inseparable mixture of raputindole A (**1**) and its monotosyl derivative was obtained.[26-30] Inspection of the ^{1}H-NMR spectrum of the crude mixture, revealed the formation of a multiplet at δ 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).

Scheme 4. Methallylation and final steps in the total synthesis of Raputindole A (1).



(a) Lewis acid (0.2 equiv of $InCl_3$, 27 h, 52%; 0.1 equiv $BiBr_3$, 1,5 h, 66%; 0.1 equiv $FeCl_3$, 1.5 h, complex mixture), DCE, rt; (b) $BiBr_3$ (0.2 equiv), DCE, rt, 1 h, 69% *cis:trans* (2:1). (c) **14** (2.0 equiv), (5*R*,7*S*)-**6** (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), NaOAc (2.0 equiv), *n*Bu_4NBr (0.2 equiv), *N,N*-dimethylacetamide:H_2O (9:1), 100 °C, dark, 24 h, 48%. (d) TsOH (1.2 equiv), toluene, 80 °C, dark, 4 h, 98%. (e) **14a**:**14b** (2.0 equiv), **15** (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), NaOAc (2.0 equiv), *n*Bu_4NBr (0.2 equiv), *N,N*-dimethylacetamide:H_2O (9:1), 100 °C, dark, 24 h, 71%. (f) NaOH (10.0 equiv), MeOH:THF (2:1), 67%, Raputindole (**1**): 6-*epi*-Raputindole A (1:2).

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-iodo-indole **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**).[17] Additionally, 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).

AUTHOR INFORMATION

Corresponding Author

pilli@iqm.unicamp.br
ORCID
Ronaldo A. Pilli: 0000-0002-5919-7763
Juliana L. L. F. Regueira: 0000-0002-2177-6524

Author Contributions

LFS conceived the original synthetic proposal.
RAP conceived the revised synthetic approach, supervised the experimental work and the writing of this communication.
JLLFR carried out all the experimental work, wrote the communication and prepared the figures.

Notes

The authors declare no competing financial interest.

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