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

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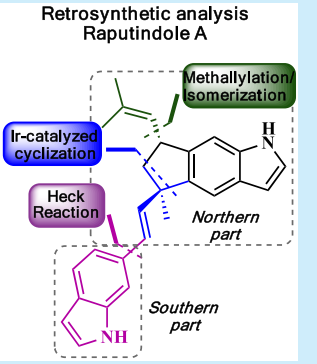
**ABSTRACT:** This work describes the total synthesis of raputindole A (**1**) through a convergent approach that features (1) an iridium-catalyzed cyclization to assemble the tricyclic core of the northern part, (2) enzymatic resolution to secure the preparation of an enantiomerically pure benzylic alcohol intermediate, and (3) the installation of the isobutenyl side chain via methallylation of the corresponding benzylic carbocation and coupling of the northern and southern parts via the Heck reaction. (+)-Raputindole A (**1**) was prepared in 10 steps (longest linear sequence) in 3.3% overall yield.






Raputindole A (**1**) was isolated in 2010 from *Raputia simullans kalunki*, a tree found in the Peruvian Amazon rainforest, along with raputindoles B (**2**), C (**3**), and D (**4**) and displayed moderate inhibitory activity of CDK2, GSK-3B, and DYRK1 kinases ($IC_{50}$ > 10 $\mu$M, Figure 1).[1] Deoxiraputindole C (**5**) is another member of this family, which was isolated in 2011 from *Raputia praetermissa*, collected in the Brazilian Amazon forest.[2] Structurally, this is a rare new class of indole alkaloid as it features unsubstituted N-1, C-2, and C-3 positions.[1] Other natural products containing the 1,2,3-unsubstituted pattern are trikentrin A[3] and the alkaloids from the herbindole family.[4] Another feature of some of the representatives of this rare alkaloid class is the presence of a linear 1,5,6,7-tetrahydrocyclopenta[*f*]indole scaffold, 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 spongotine A,[8] caulindoles,[9] and dragmacidin D,[10] which, unlike raputindoles, have their indole moieties connected via the C-3 (spongotine A and dragmacidin D) or C-5 (caulindoles) position. Because of these unusual structural features, the raputindoles have attracted the attention of natural product and synthetic chemists.[11]

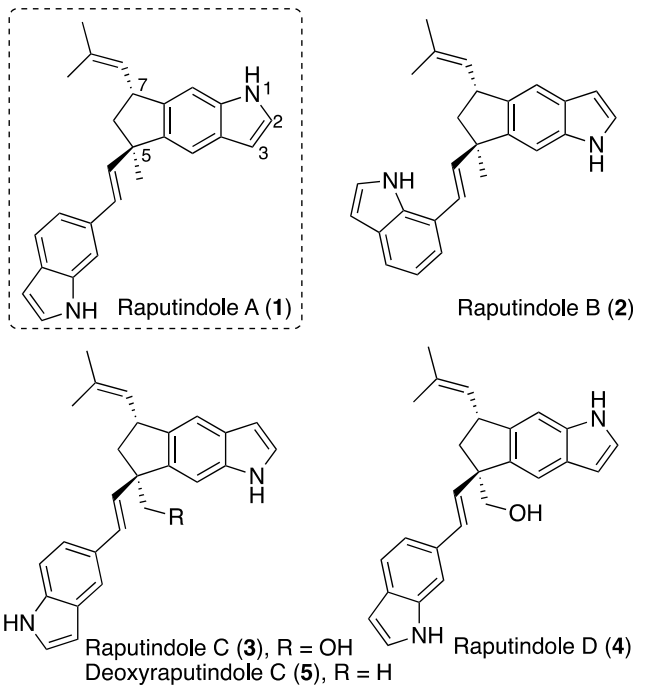



**Figure 1.** Bisindole alkaloids of the raputindole family.

The absolute stereochemistry of raputindole A (**1**) was determined in 2017, with its first total synthesis accomplished by Lindel and coworkers.[12] Their synthetic route involved a

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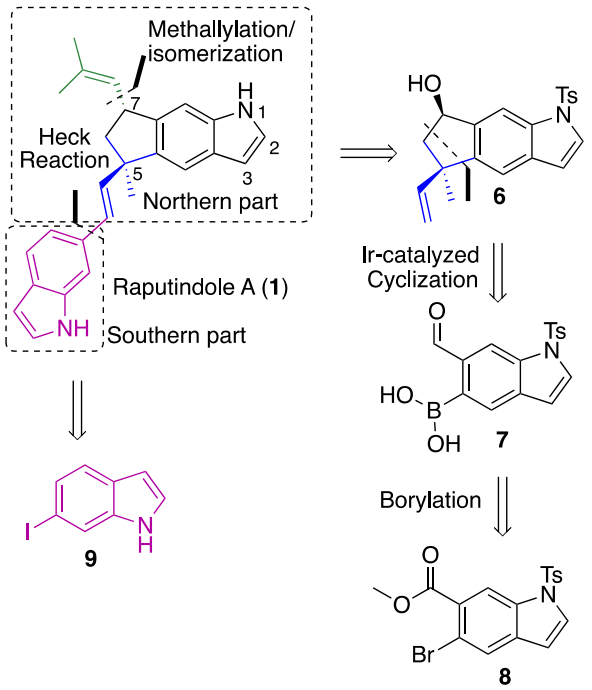
Au(I)-catalyzed cyclization to access the linear tricycle and a Pd-catalyzed installation of the isobutenyl side chain. However, low diastereoselectivity was observed in the indene catalytic hydrogenation to install the stereogenic center at C-7. To solve this critical step, in 2018, the same group published a diastereoselective total synthesis of raputindole A (**1**).[13] In addition to the Au(I)-catalyzed assembly of the cyclopentaneindole 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 because it would require additional steps, including a late-stage oxidation of an indoline intermediate. Instead, our strategy features the use of *N*-tosyl indoles in both the northern and southern parts of the structure, an iridium-catalyzed diastereoselective cyclization,[14] a methallylation reaction to install the isobutenyl side chain at C-7, and a Heck cross-coupling reaction to build the raputindole A (**1**) scaffold. It is noteworthy that our approach incorporates an enzymatic resolution step that allows us to obtain (+)-raputindole A (**1**).

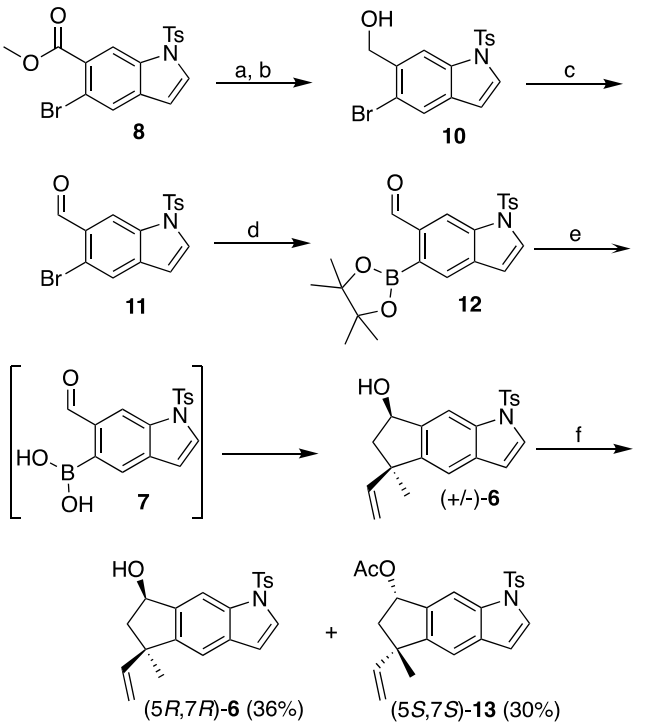
Our disconnection relies on a convergent approach where the northern and southern parts are connected via a Heck coupling reaction (Scheme 1). The isobutenyl side chain would be installed by the methallylation of the linear tricyclic indole **6** with methallyltrimethylsilane.[15] The northern part would come from boronic acid **7**, to be prepared from commercially available bromoindole **8**. An iridium-catalyzed cyclization with isoprene would provide the linear tricyclic *N*-tosyl indole **6**, according to the methodology described by Hayashi and coworkers for representative boronic acids.[14] The southern part required the use of indole **9** to be prepared via a Batcho−Leimgruber protocol.[16] This convergent approach could also allow for the total syntheses of raputindole B (**2**) and deoxiraputindole C (**5**).

**Scheme 1. Retrosynthetic Analysis for Raputindole A (1)**




The commercially available 5,6-disubstituted indole **8** was protected as the corresponding *N*-tosyl derivative, followed by the diisobutylaluminium hydride (DIBAL-H) reduction of the methyl ester and benzylic oxidation with manganese dioxide, en route to aldehyde **11** (three steps, 95% overall yield, Scheme 2). To install the necessary boronic acid, a Miyaura borylation was employed using $Pd(Cl)_2(dppf)$ and bis-(pinacolato)diboron, which provided pinacol ester **12** in 95% yield after silica gel chromatography.[17] 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, which, to the best of our knowledge, has so far not been applied to the total synthesis of a natural product. Initial attempts to use boronic acid **7** as the substrate in this cyclization provided indole **6** in 36% yield, and we then decided to explore the *in situ* generation of boronic acid **7** via the hydrolysis of pinacol ester **12**. It is worth noting that this one-pot approach proceeded regio- and diastereoselectively, providing the racemic linear tricyclic indole (±)-**6** in 94% yield as the key synthetic intermediate in our approach.[18]

**Scheme 2. Iridium-Catalyzed Preparation of Linear Tricyclic Indole (±)-6 and Its Enzymatic Resolution**[a]




[a](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, >99%. (c) $MnO_2$ (18.0 equiv), DCM, rt, 5 h, >99%. (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), $[Ir(Cl)(COD)]_2$ (0.05 equiv), $Et_3N$ (1.25 equiv), isoprene (10.0 equiv), THF/toluene (1:1), 80 °C, 24 h, 94%. (f) Vinyl acetate (4.0 equiv), CALB (2:1 mass ratio g/g), toluene/MTBE (8:2 v/v), 64 °C, 34 h, 30% of (*S*,*S*)-**13** and 36% of (*R*,*R*)-**6**, *ee* >99%.

According to the mechanistic proposal put forth by Hayashi and coworkers,[14] the formation of indolyliridium(I) species B is followed by the coordination of isoprene to the metallic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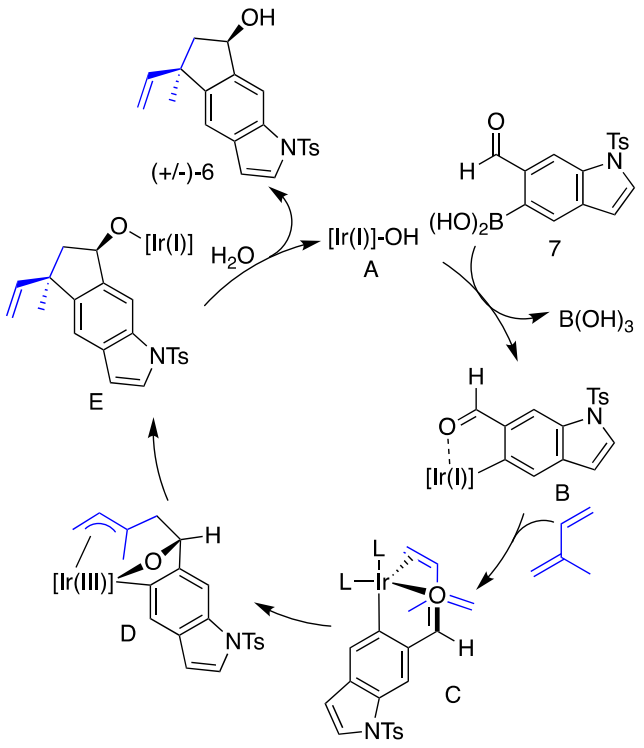
center (intermediate C) and the addition of the electron-rich terminal double bond to the activated carbonyl, leading to the $\pi$-allyliridium(III) complex D (Scheme 3). Reductive elimination affords iridium(I) alkoxide E, which is hydrolyzed to cyclopenta[*f*]indole (±)-**6** with the regeneration of the catalytic species. The relative stereochemistry depicted for (±)-**6** was confirmed later on at the stage of the bisindole **15** (Scheme 4) through the irradiation of its carbinolic proton ($\delta$ 5.38), which led to an increment in the signal of the methyl group at C-5 ($\delta$ 1.47; see the SI). Overall, the implemented six-step route afforded the racemic tricyclic *N*-tosyl indole **6** in 85% overall yield from commercially available 5,6-disubstituted indole **8**.

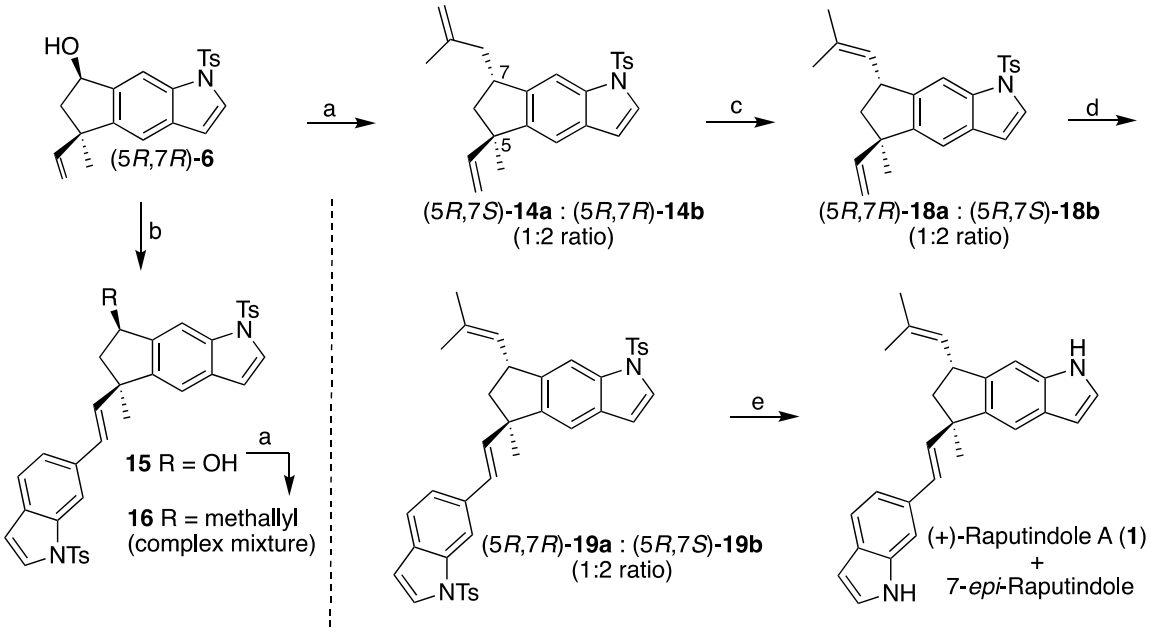
**Scheme 3. Mechanistic Proposal for the Hayashi [3 + 2] Annulation**




To secure indole **6** in enantiomerically pure form, we devised the use of the enzymatic resolution of racemic (±)-**6** with lipase B from *Candida antarctica* (CALB-Novozym 435), which is known to be very selective for the hydrolysis and transesterification of secondary alcohols, particularly in the acetylation of benzylic alcohols, as reported by Ferraz and coworkers (Scheme 2).[19] After solvent screening and optimization of enzyme loading, we found that by using a toluene/MTBE mixture (8:2 v/v) as the solvent and increasing the amount of CALB to a 2:1 mass ratio compared with the substrate, treatment of benzylic alcohol (±)-**6** with vinyl acetate provided the corresponding enantiomerically pure acetate (5*S*,7*S*)-**13** (30% yield) and enantiomerically pure alcohol (5*R*,7*R*)-**6** (36% yield, >99% *ee*, as determined by chiral HPLC; see the SI).[20,21]

To complete our synthetic approach to (+)-raputindole A (**1**), the isobutenyl side chain and the southern indole moiety needed to be installed. The former was planned to be introduced via the methallylation of the benzylic carbocation to be derived from (5*R*,7*R*)-**6** with methallyltrimethylsilane, which required the screening of different Brönsted and Lewis acids. To establish the best experimental conditions, allyltrimethylsilane was employed as a model nucleophile.

**Scheme 4. Methallylation and Final Steps in the Total Synthesis of Raputindole A (1)**[a]




[a](a) $BiBr_3$ (0.2 equiv), methallyltrimethylsilane (2.0 equiv), DCE, rt, 1 h, 69%, **14a**/**14b** (1:2 ratio). (b) **17** (2.0 equiv), (5*R*,7*R*)-**6** (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), NaOAc (2.0 equiv), $nBu_4NBr$ (0.2 equiv), *N*,*N*-dimethylacetamide/$H_2O$ (9:1), 100 °C, 24 h, 48%. (c) TsOH (1.2 equiv), toluene, 80 °C, 4 h, 98%, **18a**/**18b** (1:2 ratio). (d) **18a**/**18b** (2.0 equiv), **17** (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), NaOAc (2.0 equiv), $nBu_4NBr$ (0.2 equiv), *N*,*N*-dimethylacetamide/$H_2O$ (9:1), 100 °C, 24 h, 71%, **19a**/**19b** (1:2 ratio). (e) NaOH (10.0 equiv), MeOH/THF (2:1), 64 °C, 67%, raputindole A (**1**)/7-*epi*-raputindole A (1:2 ratio).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Whereas the use of $FeCl_3$ in dichloroethane at room temperature only led to a complex mixture, the desired allylation product could be isolated both with $InCl_3$ (52% yield) and with $BiBr_3$ (66% yield). Inspection of the $^1H$ NMR spectra of the products revealed that a 4:1 and 3:1 mixture of products, respectively, was formed.[22,23] Considering the best yields observed with bismuth tribromide in dichloroethane at room temperature, these conditions were employed with methallyltrimethylsilane as the nucleophile, and a mixture of methallyl-substituted indoles (5*R*,7*S*)-**14a** and (5*R*,7*R*)-**14b** was isolated in 69% yield as a 1:2 molar ratio. In an attempt to improve the ratio in favor of the required (5*R*,7*S*)-**14a**, a second approach was also investigated where the order of the two key steps was reversed. A Heck reaction of (5*R*,7*R*)-**6** with *N*-tosyl 6-iodoindole (**17**), prepared according to the literature procedure,[24] provided bisindole (5*R*,7*R*)-**15** in 48% yield. Unfortunately, attempts to perform the bismuth-tribromide-mediated methallylation were unsuccessful, providing only a complex mixture containing the desired product **16** (Scheme 4).

Despite the poor diastereoselectivity observed in the installation of the isobutenyl side chain, we moved forward with the 1:2 mixture of (5*R*,7*S*)-**14a** and (5*R*,7*R*)-**14b** and proceeded to the isomerization to convert the exo double bond to the required isobutenyl side chain. Treatment with *p*-TsOH in toluene at 80 °C afforded a 1:2 mixture of (5*R*,7*R*)-**18a** and (5*R*,7*S*)-**18b** in >99% yield.[25] With the northern and southern moieties secured, the mixture of indoles **18a** and **18b** was submitted to the Heck reaction conditions already employed for (5*R*,7*R*)-**6** to provide a 1:2 mixture of (5*R*,7*R*)-**19a** and (5*R*,7*S*)-**19b** in 71% yield. The removal of both tosyl groups, which have served well for the assembly of the key bisindole precursor, was a challenging undertaking. Initially, we attempted to use TBAF in THF, thioglycolic acid, as well as LiOH in THF to remove the tosyl groups, but we only observed product degradation. The use of KOH and CTAB in THF-$H_2O$ under phase-transfer catalysis made the deprotection possible, but an inseparable mixture of raputindole A (**1**) and its monotosyl derivative was obtained.[25−30] An inspection of the $^1H$ NMR spectrum of the crude mixture, revealed the presence of a multiplet at $\delta$ 6.51 to 6.53, which correlates with the one observed in 6-iodo-indole (**9**), suggesting the deprotection of the southern indole moiety. This conclusion was also corroborated by nuclear Overhauser effect spectroscopy (NOESY) analysis of the crude mixture. After extensive experimentation, we found out that NaOH in THF/MeOH at 64 °C was the best condition to remove both tosyl groups, providing a 1:2 mixture of raputindole A (**1**) and its C-7 epimer in 67% yield, which were separated by preparative chiral HPLC (Chiralpak IA column) to afford (+)-raputindole A (**1**), which was spectroscopically identical to the natural product. (See the SI.)

In summary, we have accomplished the diastereoselective total synthesis of (+)-raputindole A (**1**) through stereoselective iridium-catalyzed cyclization, enzymatic resolution, and methallylation promoted by bismuth tribromide followed by isomerization, which allowed the northern part of raputindole A (**1**) to be obtained as a 1:2 mixture of (5*R*,7*R*)-**18a** and (5*R*,7*S*)-**18b**. After merging it with the southern part, represented by *N*-tosyl 6-iodo-indole (**17**), via the Heck reaction and the removal of both tosyl groups, (+)-raputindole A (**1**) was isolated in 10 steps (longest linear sequence) in 3.3% overall yield after preparative chiral HPLC separation.

The approach described herein should also be amenable for the preparation of (±)-raputindole A (**1**) in nine steps from the commercially available 6-iodo indole (**9**) in a comparable yield as that reported in its first synthesis[12] and at the same time offering a much shorter route than the one reported in the second synthesis of (±)-raputindole A (**1**).[13]

Despite the still unresolved control of the stereochemistry at C-7, the originality of our approach stems from the efficient preparation of the tricyclic indole (±)-**6** in 85% overall yield from the commercially available indole **8** and its versatility from the availability of a chiral version of the iridium catalyst to develop an asymmetric synthesis of raputindole A (**1**).[18] 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 (**5**) as well as to derivatives thereof to support structure−biological activity relationship studies.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01943.

Experimental procedures and spectral data for all new compounds (PDF)

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### Author Contributions

L.F.S. conceived the original synthetic proposal. R.A.P. conceived the revised synthetic approach and supervised the experimental work and the writing of this Letter. J.L.L.F.R. carried out all the experimental work and wrote the Letter.

### Notes

The authors declare no competing financial interest.

[§]L.F.S.: In memoriam.

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contributed to the final route. We thank Professor Leandro H. Andrade (USP) for kindly providing the enzyme CALB and allowing the access to GC-MS equipment, Professor Fernando Antônio Santos Coelho (UNICAMP) for providing the preparative Chiralpak column, and Professor Helio Alexandre Stefani (USP) for allowing access to preparative HPLC. R.A.P. dedicates this work to his former Ph.D. advisor, Professor Albert J. Kascheres, for his mentoring, guidance, and example.

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