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Total Synthesis of Exiguamines A and B Inspired by Catecholamine Chemistry

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Abstract: The evolution of a total synthesis of the exiguamines, two structurally unusual natural products that are highly active inhibitors of indolamine-2,3-dioxygenase (IDO), is described. The ultimately successful strategy involves advanced cross-coupling methodology and features a potentially biosynthetic tautomerization/electrocyclization cascade reaction that forms two heterocycles and installs a quaternary ammonium ion in a single synthetic operation.

Keywords: biomimetic synthesis · cross-coupling · dopamines · electrocyclic reactions · total synthesis

Introduction

Indolamine-2,3-dioxygenase (IDO) catalyzes the first and rate-limiting step in the metabolic degradation of tryptophan and has emerged as an interesting target in antitumor therapy.[1,2] This is because solid tumors, such as cervical cancers, evade the immune response by decreasing local concentrations of tryptophan, which is essential for the activation of killer T-lymphocytes. As such, IDO inhibitors, which would increase the concentration of tryptophan and allow for the staging of an effective immune response, have great potential in antitumor therapy.

The best established, albeit weak, IDO inhibitor is 1-methyltryptophan (Figure 1).[3] Recently several other inhibitors with increased activities have emerged, including methyl thiohydantoin tryptophan[4] and the natural products plectosphaeroic acid A[5] as well as annulin B[6] (Figure 1). Alkaloid exiguamine A, isolated from the marine sponge *Neopetrosia exigua*, was found to be the most potent inhibitor ($K_i = 41 \pm 3$ nM) of IDO to date.[7,8]

In addition to its potent bioactivity and potential as a lead compound for drug development, certain structural features render exiguamine A an attractive candidate for total synthesis. The molecule, which was isolated in racemic form, possesses a unique hexacyclic skeleton with a variety of nitrogen and oxygen functionalities. It contains an indolequinone and an *N*,*N*-dimethyl dihydroindolinium moiety, both of which are fused to a central spirobicyclic ring system that contains a hydantoin and a pyran ring. An abundance of polar functionalities that include a primary amine, a phenol and a quaternary ammonium ion also make exiguamine A a challenging target.

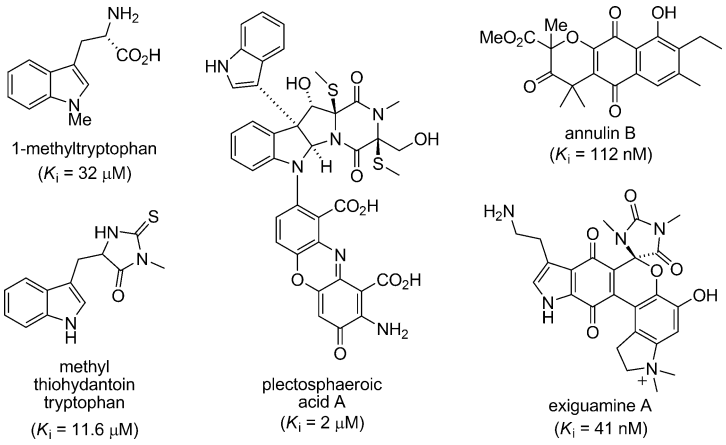

Figure 1. Indolamine 2,3-deoxygenase inhibitors and their activities.

In our opinion, the unusual structural and physicochemical features of the molecule can be best met with a synthetic approach that draws heavily from biosynthetic considerations. This is particularly true with respect to the spirohydantoin moiety and the quaternary ammonium ion. To test the projected biomimetic key steps, we needed to synthesize novel indole and dopamine-derived building blocks and couple them to produce complex biaryl intermediates. We now report how a successful synthetic strategy gradually emerged under these guidelines and provide full details of our various routes, which ultimately converged in a total synthesis of exiguamine A and allowed for the elucidation of a naturally occurring congener.[9]

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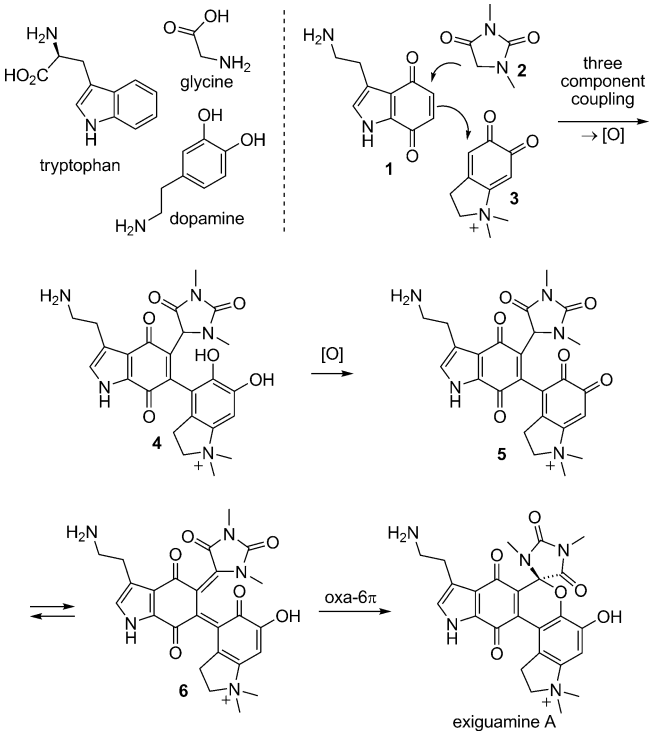
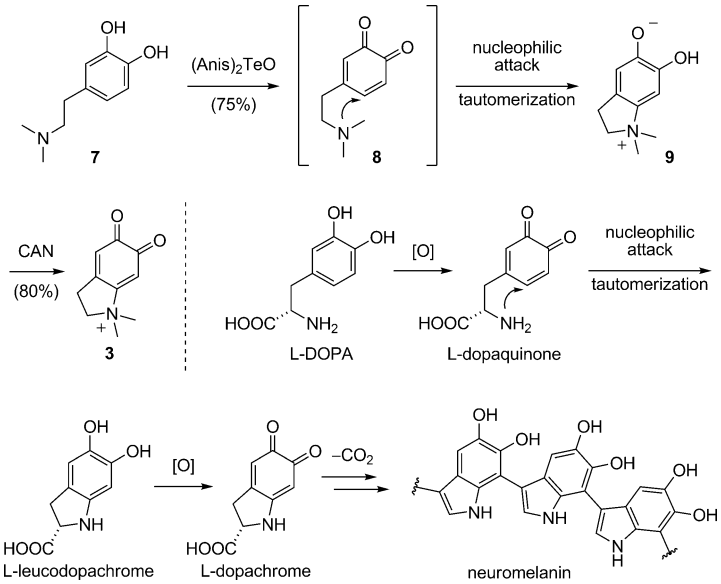
Results and Discussion

Initial planning and studies toward exiguamine A: Biosynthetically, exiguamine A appears to originate from tryptophan, glycine, and dopamine, the latter also occurs in *N. exigua* (Scheme 1). We envisaged that three related building blocks, namely indole quinone **1**, *N*,*N*-dimethylhydantoin (**2**), and *ortho*-quinone **3**, could be joined in a three component coupling to afford the molecular skeleton of exiguamine A in a single step. Nucleophilic addition of the hydantoin enolate to *para*-quinone **1**, followed by trapping with the highly electrophilic *ortho*-quinone **3** and air oxidation would afford **4**. Another oxidation would then yield bisquinone **5**, which would undergo tautomerization to *ortho*-quinone methide **6** and oxa-6π electrocyclization to produce exiguamine A. Similar tautomerization/electrocyclization cascades have been investigated in detail in our group and have been implemented in total syntheses, for instance in the total synthesis of the microphyllaquinone.[10] Alternatively, exiguamine A could be formed from **4** through an oxidative cyclization that involves radicals. In any case, we felt that **4** was a reasonable synthetic—and potentially biosynthetic—intermediate and therefore focused our efforts on its preparation.

To put this plan into practice, the known *N*,*N*-dimethyldopamine **7** was oxidized to afford dihydroindolinium catechol **9**.[11] This reaction presumably proceeds via formation of the *ortho*-quinone **8**, which then undergoes intramolecular nucleophilic attack by the appended tertiary amine. Further oxidation of **9** in the presence of ceric ammonium nitrate (CAN) then gave *ortho*-quinone **3** (Scheme 2). This oxidative chemistry resembles the initial steps in the formation of melanin, which is triggered by oxidation of a catecholamine (e.g., L-DOPA) to the corresponding *ortho*-quinone (e.g., L-dopaquinone), followed by intramolecular nucleophilic attack of the α-amino group, tautomerization, further oxidation, and, ultimately, polymerization (Scheme 2).[12] It can be reasonably assumed that a similar series of steps takes place in the biosynthesis of exiguamine A. Indeed, a similar key step has been used in a biomimetic total synthesis of an alkaloid anachelin H, wherein the cyclization was catalyzed by the enzyme tyrosinase.[13]



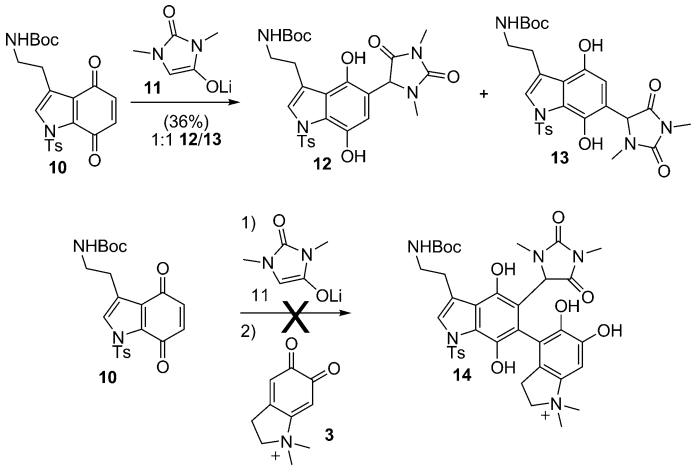
Scheme 1. Original synthetic plan.



Scheme 2. Oxidative cyclizations of catecholamines.

Following the protocol of Heathcock, we then quickly gained access to gram quantities of the requisite protected indoloquinone **10**.[14] Subjecting *para*-quinone **10** to the lithium enolate of hydantoin **11**[15] provided a 1:1 mixture of hydantoin adducts **12** and **13** whose regiochemistry could not be unambiguously assigned, in 36% combined yield (Scheme 3). While a literature report suggested that removal of the electron withdrawing tosyl group from the indole nitrogen of **10** might improve the regioselectivity of the addition,[16] we were unable to access the free indole either by deprotection of *para*-quinone **10** or oxidation of an unprotected 4,7-dimethoxy tryptamine. More importantly, reaction of indoloquinone **10** with the lithium enolate of **11**, followed by the addition of *ortho*-quinone **3**, failed to provide the desired hydroquinone **14**. We quickly realized that a revised synthetic plan was needed.

Revised synthetic plan: Our failure to effect the three-component coupling and the ease with which the quaternary ammonium ion **3** could be synthesized through oxidative catecholamine chemistry led us to revise the endgame of the synthesis. We decided that quinone **15**, wherein the quater-

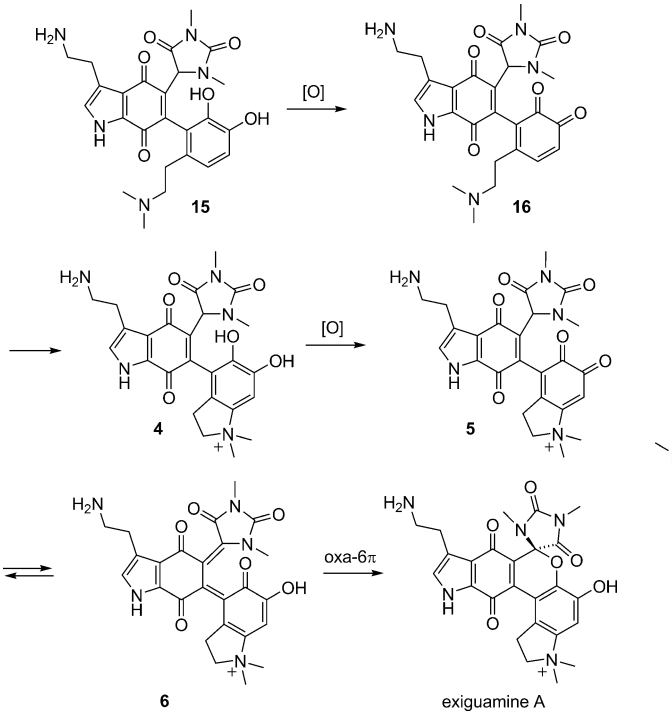


Scheme 3. Failed three-component coupling.

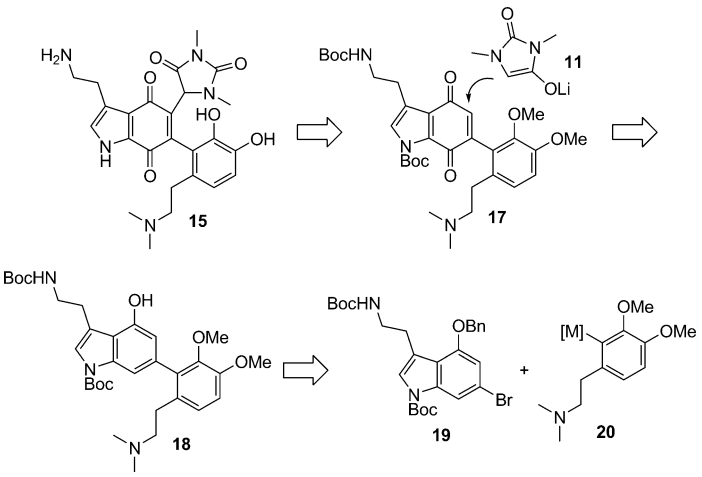
nary ammonium ion is not formed, would be a more strategic synthetic precursor of exiguamine A (Scheme 4). Presumably, oxidation to bisquinone **16**, followed by intramolecular nucleophilic attack by the tertiary amine and subsequent tautomerization, would give catechol **4**. A second oxidation (→**5**) followed by tautomerization would provide *ortho*-quinone methide **6**, which would undergo *oxa*-6π electrocyclization to afford exiguamine A.

Thus, the spirohydantoin and the quaternary ammonium ion would be installed in one final event, which could potentially take place in the actual biosynthesis as well.

This revised endgame allowed us to postpone the handling of the difficult quaternary ammonium ion until the final step, but it also resulted in a less convergent approach to the key precursor. However, the regioselectivity issues of the hydantoin addition could be avoided by adding the enolate of *N*,*N*-dimethylhydantoin (**11**) to aryl *para*-quinone **17** (Scheme 5). Indole quinone **17** could be obtained by a regioselective oxidation of phenol **18**, which could in turn be synthesized via transition metal catalyzed cross-coupling from a relatively simple bromotryptamine **19** and the suitably functionalized dopamine derivative **20**. This choice of coupling partners would presumably minimize steric issues in the transition metal-mediated cross-coupling step.

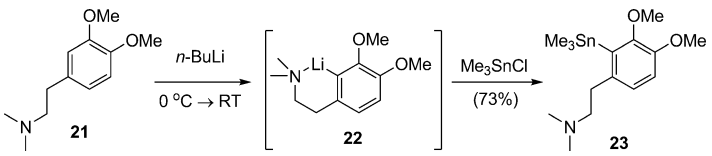


Scheme 4. Revised endgame.



Scheme 5. Retrosynthetic analysis of the key intermediate **15**.

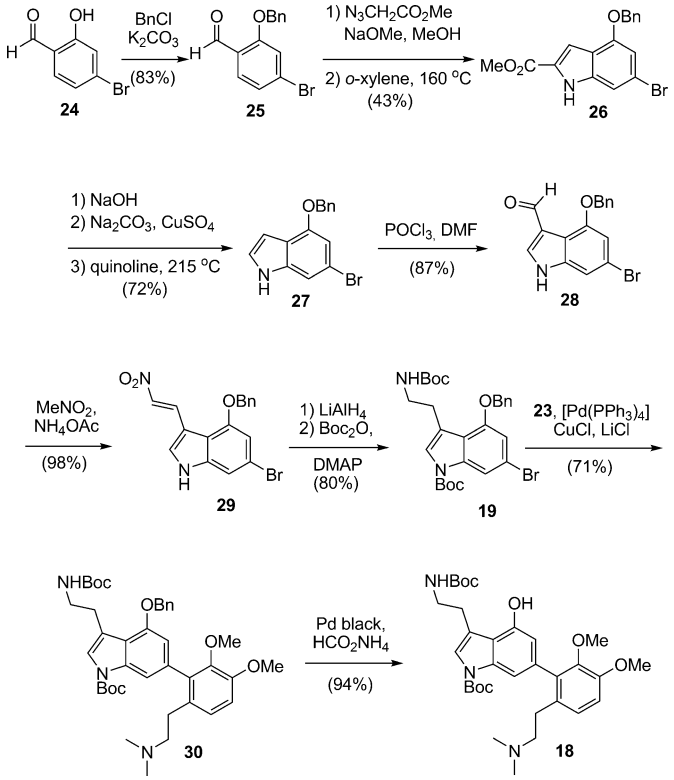
The phenethylamine cross-coupling partner **23** was synthesized by the directed lithiation of known dopamine derivative **21**[17] under equilibrating conditions,[18] followed by trapping of the aryl lithium intermediate **22** with trimethyltin chloride (Scheme 6). Interestingly, while the metalation of benzylamines and benzoyl amides is well established, the regioselective metalation of phenethylamines is comparatively rare, despite the enormous importance of this pharmacophore in medicinal chemistry. Preliminary experiments show that **23** is indeed a valuable precursor of 3-substituted dopamine derivatives that could serve as D_2-receptor agonists.[19]



Scheme 6. Synthesis of a metalated dopamine derivative.

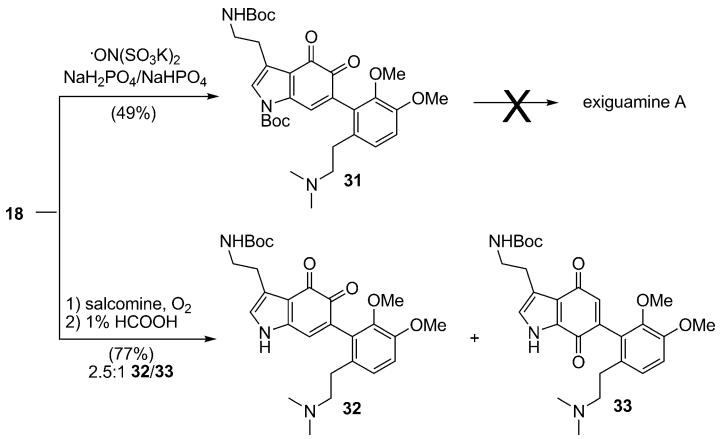
The tryptamine cross-coupling partner **19** was synthesized starting from the commercially available bromosalicylaldehyde **24** (Scheme 7). Benzyl protection (→**25**), followed by condensation with methyl azidoacetate and subsequent Hemetsberger indole cyclization, provided 2-carbomethoxyindole **26** in good overall yield.[20] Subsequent saponification

and copper(II)-mediated decarboxylation in quinoline solution afforded indole **27**.[21] Formylation (→**28**), Henry reaction (→**29**), reduction, and protection of the nitrogen atoms then gave the target tryptamine **19**.[22] The stage was now set to form the critical biaryl bond via Stille cross-coupling. Indeed, reaction of **19** with **23** under Corey's conditions gave the protected biaryl **30** in good overall yield.[23] Debenzylation then proceeded without incident to give phenol **18**, which was intended to serve as a precursor of the requisite indole quinone **17**.



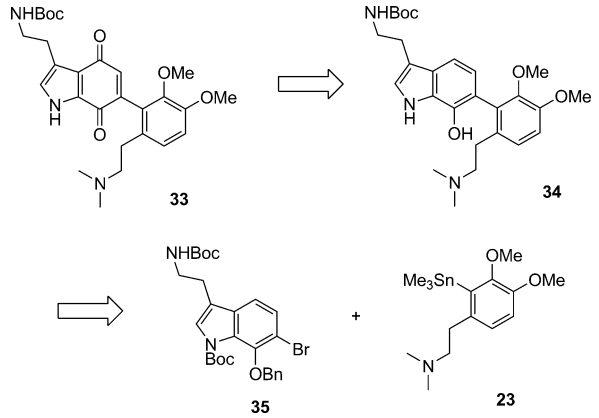
Scheme 7. Synthesis of a key biaryl intermediate.

From the outset, we envisaged a regioselective oxidation of **18** to the *para*-quinone **17** using Fremy's salt (potassium nitrosodisulfonate) as the oxidant,[24] which was well precedented in the literature.[14,25] We found, however, that subjection of phenol **18** to Fremy's salt in a 1:1 mixture of ethyl acetate and phosphate buffer gave exclusively the *ortho*-quinone **31** (Scheme 8). Although we were initially unable to assign the structure of **31** with certainty, our inability to convert it into exiguamine led us to believe that **31** was indeed an *ortho*-quinone and not the desired *para*-quinone. Therefore, we subjected phenol **18** to salcomine under an oxygen atmosphere to provide a mixture of the corresponding *ortho*- and *para*-quinones, respectively. These regioisomers could be separated using reversed-phase chromatography, only after selective cleavage of the indole Boc group under mild conditions, yielding **32** and **33**. Unfortunately, the desired regioisomer, *para*-quinone **33**, was isolated as the minor product, even after extensive optimization of the reaction conditions.



Scheme 8. Oxidative formation of quinones.

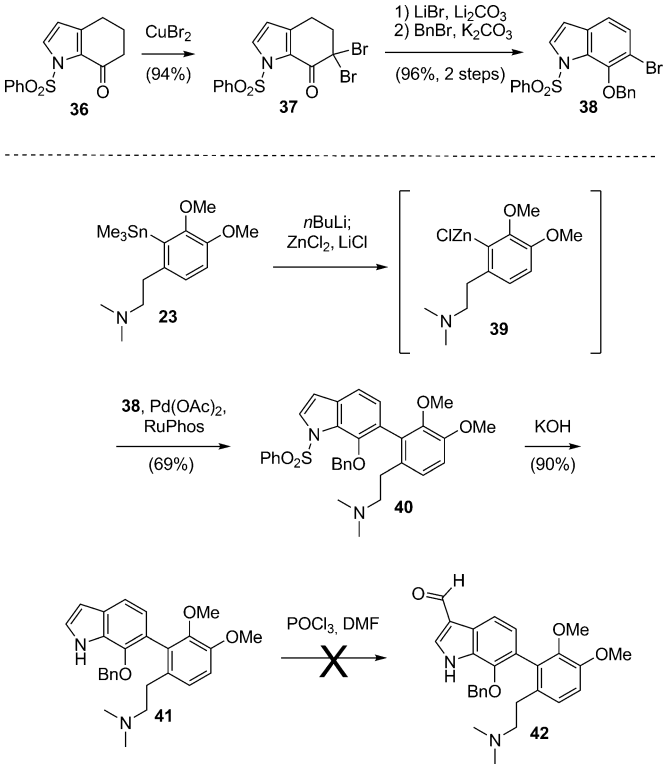
Final synthetic plan: Although the *para*-quinone **33** could be obtained in sufficient quantities for the progression of the synthesis, we were not satisfied with the poor regioselectivity of the oxidation and sought an alternative approach. One way to address this problem would be the use of phenol **34**, a regioisomer of **18** (Scheme 9). This, in turn, could be assembled via cross coupling of our aryl stannnane **23** with bromo indolamine **35**, an analogue of **19**. Although this strategy would overcome regioselectivity issues it would require a much more challenging biaryl coupling due to the presence of three *ortho*-substituents.



Scheme 9. Retrosynthetic analysis of the key *para*-quinone **33**.

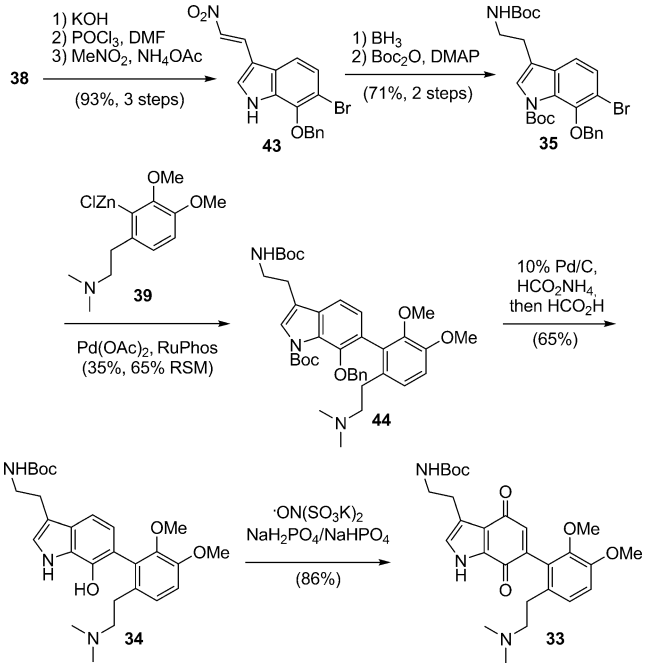
7-Hydroxy indole derivatives of type **35** are rarely found in the literature and difficult to access with established indole chemistry,[26] including modern transition metal-mediated methodologies. We therefore decided to use a comparatively rare strategy that involves aromatization of a partially saturated six-membered ring (Scheme 10).[27] To this end, the known pyrrolo cyclohexenone **36** was doubly brominated and fully aromatized through elimination of HBr, then protected as a benzyl ether to yield 7-hydroxy-6-bromoindole derivative **38**.[28] All attempts to couple this compound with dopamine-derived stannane **23** via Stille coupling were

futile. However, the corresponding Negishi coupling with the organozinc halide derived from **23** was more successful. After careful optimization, we found that this step could be carried out in the presence of RuPhos to yield the sterically congested biaryl **40** in good yield.[29] Desulfonylation of this compound then gave indole **41**.[30] Unfortunately, we were unable to cleanly functionalize this compound at the 3-position of the indole, presumably due to numerous nucleophilic positions elsewhere in the molecule.



Scheme 10. Development of the Negishi coupling route.

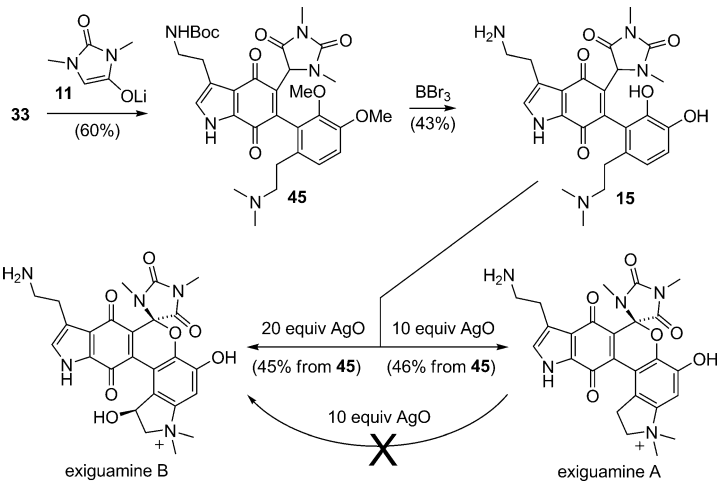
To overcome this issue and to increase the convergence of the synthesis we decided to install the ethylamine side chain before the cross-coupling. To this end, **38** was desulfonylated, formylated, and condensed with nitromethane to yield nitrovinylindole **43** (Scheme 11).[9] Chemoselective reduction of the nitrovinyl moiety in the presence of the aryl bromide proved challenging, but could be eventually effected with borane in THF.[31] Protection of the resulting primary amine as a *tert*-butyl carbamate then gave **35**, which could be coupled with organozinc chloride **39** under similar conditions as before. The resulting biaryl **44** was then debenzylated to afford 7-hydroxyindole **34**. As anticipated, the oxidation now proceeded cleanly to yield the key indole *para*-quinone **33**. Interestingly, the indole nitrogen had to be deprotected for the oxidation to take place, once again highlighting how sterically crowded the biaryl molecule is. Despite the modest yield of the cross-coupling reaction, which was more satisfying considering that the unreacted starting material could be fully recovered and recycled, this second generation synthesis to **33** benefits from a regioselective oxidation to install the *para*-quinone and it is also more convergent.



Scheme 11. Regioselective synthesis of biaryl *para*-quinone **33**.

Synthesis of exiguamine A and discovery of exiguamine B: In the final phase of our synthesis, *para*-quinone **33** was subjected to a large excess of the lithium enolate of *N*,*N*-dimethylhydantoin **11** (Scheme 12).[9] After aqueous workup in the presence of air, we isolated *para*-quinone **45**. Removal of all remaining protecting groups using BBr_3 proceeded uneventfully to give **15**, the centerpiece of our synthetic plan and biosynthetic proposal.

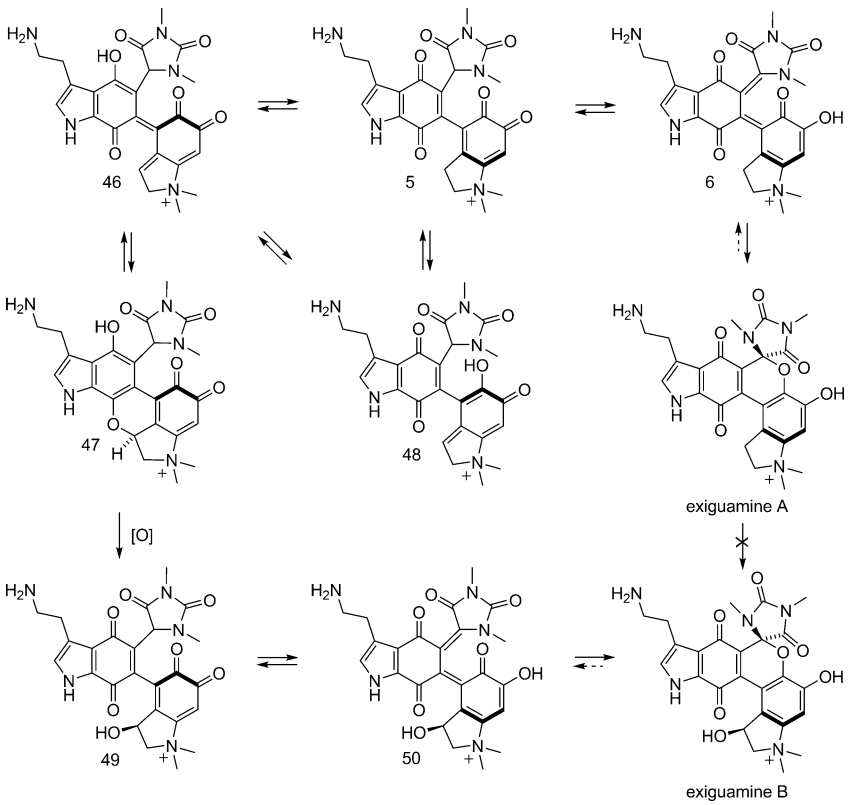
Treatment of the crude product with ten equivalents of silver(II) oxide suspended in 2% formic acid in methanol gave exiguamine A in 46% yield.[32] This single synthetic operation presumably includes two oxidations, the intramolec-



Scheme 12. Synthesis of exiguamine A and discovery of exiguamine B.

ular nucleophilic attack of a tertiary amine onto an *ortho*-quinone, tautomerization, and finally *oxa*-6π-electrocyclization, as shown in Scheme 4. The use of silver(II) oxide proved essential to promote this reaction cascade, as subjection of crude **15** to an ambient oxygen atmosphere along with other oxidation conditions failed to oxidize the catechol moiety and resulted in the recovery of pure **15**.

Our efficient synthesis of exiguamine A yielded enough material for extensive biological testing and allowed us to determine the K_i of the natural product. It also gave us an opportunity to further explore the fascinating chemistry of catecholamines. During attempts to improve the yield of the final step, we treated crude **15** with a twenty-fold excess of silver(II) oxide. Under these conditions, we noticed the formation of a new product in addition to trace amounts of exiguamine A. This compound was isolated in 45% yield and was identified as exiguamine B, a hydroxylated derivative of exiguamine A (Scheme 12). Notably, exiguamine B was not found when exiguamine A was resubjected to our standard oxidative conditions. Exiguamanie B contains structural features of other important catecholamines, such as adrenaline and noradrenaline, which are formed biosynthetically through enzymatic hydoxylations of the benzylic position.



Scheme 13. Proposed biosynthetic relationship of exiguamine A and B.

At this stage, we became aware that the name of exiguamine A implies the existence of other exiguamines (exiguamine B, C, etc.). We therefore contacted the isolation group with our spectral data and were happy to learn that our hydroxylated byproduct was indeed identical to a natural product, namely exiguamine B, which had only been obtained in minute quantities from natural sources. Using our synthetic product, the relative stereochemistry of exiguamine B could be clarified by NOE measurements.[9]

Proposed biosynthesis of exiguamine B: To account for the formation of exiguamine B, both in the laboratory and in nature, we propose that it is also a product derived from bisquinone **5**, which is in equilibrium with its tautomers **6**, **46**, and **48** (Scheme 13). A reversible oxa-6π electrocyclization of **46** would then afford **47** and place an oxygen functionality at the benzylic position. In the presence of a large excess of oxidant (20 instead of 10 equivalents of AgO), **47** is intercepted via an oxidation to yield hydroxylated bisquinone **49**. Tautomerization to vinyl *ortho*-quinone methide **50**, followed by *oxa*-6π electrocyclization would then yield exiguamine B, in analogy to exiguamine A. In line with our hypothesis, resubjection of exiguamine A to excess AgO did not yield exiguamine B. This seems to rule out an alternative mechanism that would involve nucleophilic attack of water onto a *para*-quinone methide.

We have previously demonstrated that tautomerizations and electrocyclizations of the type shown in Scheme 13 are surprisingly facile and are associated with low kinetic barriers.[10] In order to probe the reversibility of the individual steps proposed herein, we performed a density functional theory study (B3LYP/6-31G**,[33–35] Jaguar 6.5).[36] The differences in electronic energies (E) of **5**, **6**, **46**, **47**, and **48** were found to be no more than 12 kcal mol^{-1} (see Supporting Information). By contrast, exiguamine A is energetically favored over **6** by 30 kcal mol^{-1}. Once formed, **5** will, thus, provide a complex mixture of tautomers **5**, **6**, **46**, and **48**, which ultimately converges on exiguamine A. Since the *oxa*-6π electrocyclization to afford dihydropyran **47** is reversible, the pathway to exiguamine B is revealed only upon oxidation to **49**.

Conclusion

In summary, we have presented the evolution of a synthetic plan that yielded two complex natural products with many novel structural and functional features. Our synthetic

design was heavily influenced by biosynthetic considerations, in particular with respect to pericyclic reactions and catecholamine chemistry. While the proposed tautomerization and electrocyclization cascades are somewhat speculative, but strongly supported by the DFT calculations, the oxidative cyclization of a tertiary catecholamine most likely occurs in the biosynthesis as well. Indeed, we propose that compound **15** is an actual biosynthetic intermediate and could be found in the sponge as well. Whether the oxidative cyclization of this compound requires enzymatic assistance or could occur spontaneously remains to be determined. As an added benefit of our synthesis of exiguamine A, we obtained a synthetic sample of its hydroxy congener exiguamine B, which allowed for the full structural elucidation of the natural product. We hypothesize that exiguamine B also arises through oxidations and tautomerizations, and not via direct C,H-functionalization of exiguamine A or nucleophilic attack onto a *para*-quinone methide. Taken together, our various synthetic approaches also highlight the challenges that sterically congested biaryls still represent in the era of modern transition metal-catalyzed cross-coupling chemistry.

Experimental Section

Experimental procedures, characterization data, ^{1}H NMR spectra, and DFT calculations: see the Supporting Information.

Acknowledgements

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[1] C. A. Opitz, W. Wick, L. Steinman, M. Platten, *Cell. Mol. Life Sci.* **2007**, *64*, 2542–2563.
[2] a) X. Liu, R. C. Newton, S. M. Friedman, P. A. Scherle, *Curr. Cancer Drug Targets* **2010**, *10*, 938–952; b) S. Löb, A. Koenigsrainer, H.-G. Rammensee, G. Opelz, P. Terness, *Nat. Rev. Cancer* **2009**, *9*, 445–452.
[3] H. Sugimoto, S. I. Oda, T. Otsuki, T. Hino, T. Yoshida, Y. Shiro, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 2611–2616.
[4] A. J. Muller, J. B. DuHadaway, P. S. Donover, E. Sutanto-Ward, G. C. Prendergast, *Nat. Med.* **2005**, *11*, 312–319.
[5] G. Carr, W. Tay, H. Bottriell, S. K. Andersen, A. G. Mauk, R. J. Andersen, *Org. Lett.* **2009**, *11*, 2996–2999.
[6] A. Pereira, E. Vottero, M. Roberge, A. G. Mauk, R. J. Andersen, *J. Nat. Prod.* **2006**, *69*, 1496–1499.
[7] H. C. Brastianos, E. Vottero, B. O. Partick, R. Van Soest, T. Matainaho, A. G. Mauk, R. J. Andersen, *J. Am. Chem. Soc.* **2006**, *128*, 16046–16047.
[8] G. Carr, M. K. W. Chung, A. G. Mauk, R. J. Andersen, *J. Med. Chem.* **2008**, *51*, 2634–2637.
[9] M. Volgraf, J.-P. Lumb, H. C. Brastianos, G. Carr, M. K. W. Chung, M. Münzel, A. G. Mauk, R. J. Andersen, D. Trauner, *Nat. Chem. Biol.* **2008**, *4*, 535–537 and references therein.
[10] J.-P. Lumb, D. Trauner, *Org. Lett.* **2005**, *7*, 5865–5868.
[11] a) J. F. Carpenter, *J. Org. Chem.* **1993**, *58*, 1607–1609; b) J. Clews, C. J. Cooksey, P. J. Garratt, E. J. Land, C. A. Ramsden, P. A. Riley, *J. Chem. Soc. Perkin Trans. 1* **2000**, *24*, 4306–4315.
[12] A. Gaeta, R. C. Hider, *Br. J. Pharmacol.* **2009**, *146*, 1041–1059.
[13] K. Gademann, Y. Bethuel, H. H. Locher, C. Hubschwerlen, *J. Org. Chem.* **2007**, *72*, 8361–8370.
[14] K. M. Aubart, C. H. Heathcock, *J. Org. Chem.* **1999**, *64*, 16–22.
[15] G. Guella, I. Mancini, H. Zibrowius, F. Pietra, *Helv. Chim. Acta* **1988**, *71*, 773–782.
[16] Y. A. Jackson, A. D. Billimoria, E. V. Sadanandan, M. P. Cava, *J. Org. Chem.* **1995**, *60*, 3543–3545.
[17] R. J. Borgman, J. J. Mcphilli, R. E. Stitzel, I. J. Goodman, *J. Med. Chem.* **1973**, *16*, 630–633.
[18] C. D. Liang, *Tetrahedron Lett.* **1986**, *27*, 1971–1974.
[19] V. Sofiyev, "Synthetic studies of the Thio-Nazarov Cyclization. Biomimetic Total Syntheses of Shimalactones and Exiguamines. Synthesis of Photoswitchable Dopamine Analogs", Ph.D. dissertation, University or California, Berkeley, **2010**.
[20] a) R. E. Adams, J. B. Press, E. G. Degan, *Synth. Commun.* **1991**, *21*, 675–681; b) J. B. Blair, D. Kurrasch-Orbaugh, D. Marona-Lewicka, M. G. Cumbay, V. J. Watts, E. L. Barker, D. E. Nichols, *J. Med. Chem.* **2000**, *43*, 4701–4710.
[21] E. Piers, R. K. Brown, *Can. J. Chem.* **1962**, *40*, 559–561.
[22] V. Bénéteau, T. Besson, *Tetrahedron Lett.* **2001**, *42*, 2673–2676.
[23] X. J. Han, B. M. Stoltz, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
[24] H. Zimmer, D. C. Lankin, S. W. Horgan, *Chem. Rev.* **1971**, *71*, 229–246.
[25] A. Poumaroux, Z. Bouaziz, M. Domard, H. Fillion, *Heterocycles* **1997**, *45*, 585–596.
[26] G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1* **2000**, *7*, 1045–1075.
[27] a) M. Tani, T. Ariyasu, M. Ohtsuka, T. Koga, Y. Ogawa, Y. Yokoyama, Y. Murakami, *Chem. Pharm. Bull.* **1996**, *44*, 55–61; b) Y. Izawa, D. Pun, S. Stahl, *Science* **2011**, *333*, 209–213.
[28] a) A. Zelikin, V. R. Shastri, R. Langer, *J. Org. Chem.* **1999**, *64*, 3379–3380; b) M. Kakushima, P. Hamel, R. Frenette, J. Rokach, *J. Org. Chem.* **1983**, *48*, 3214–3219.
[29] G. Manolikakes, M. A. Schade, C. M. Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765–2768.
[30] P. M. Jackson, C. J. Moody, *Tetrahedron* **1992**, *48*, 7447–7466.
[31] a) L. S. Santos, R. A. Pilli, V. H. Rawal, *J. Org. Chem.* **2004**, *69*, 1283–1289; b) R. W. Schumacher, B. S. Davidson, *Tetrahedron* **1999**, *55*, 935–942.
[32] H. Sobotka, J. Austin, *J. Am. Chem. Soc.* **1951**, *73*, 3077–3079.
[33] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
[34] S. H. Vosko, L. Wilk, M. Nusair, *Can. J. Phys.* **1980**, *58*, 1200–1211.
[35] P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627.
[36] Jaguar, version 6.5, Schrödinger, LLC, New York, NY, **2006**.

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