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Stereoselective Synthesis of the Diazonamide A Macrocyclic Core

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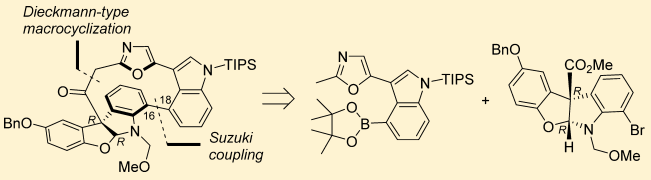
Supporting Information

ABSTRACT: Stereoselective synthesis of the right-hand heteroaromatic macrocycle of diazonamide A features C16−C18 bond formation in the Suzuki−Miyaura cross-coupling and atropodiastereoselective Dieckmann-type macrocyclization as key steps. The Suzuki−Miyaura cross-coupling gave the best yields when it was catalyzed by a palladium−dioxygen complex.



INTRODUCTION

Diazonamide A, a marine metabolite isolated from the colonial ascidian *Diazona angulata* exerts nanomolar cytotoxicity against human tumor cell lines.[1] The recent discovery of a novel mechanism of action of diazonamide A[2] has opened the door to a rational design of its simplified analogues as potential clinical agents. Not surprisingly, total synthesis of diazonamide A remains a focus of intense research efforts.

Diazonamide A contains many synthetically challenging structural elements such as a quaternary C10 stereocenter and two fused macrocycles: the left-hand 12-membered peptide ring and a right-hand heteroaromatic macrocycle possessing three axially chiral biaryl bonds (Scheme 1). Since 2002,[3] considerable synthetic efforts have resulted in four completed total syntheses[4−7] and several formal total syntheses[8] of diazonamide A. The synthetic strategy of the Harran,[4a] Nicolaou,[5] and MacMillan[7] total syntheses relied on the construction of the left-hand peptide ring prior to the formation of the right-hand heteroaromatic macrocycle. The right-hand heteroaromatic ring closure has been achieved by atropodiastereoselective formation of the C16−C18 biaryl bond using either photochemical Witkop-type cyclization (Harran, Nicolaou) or Pd-catalyzed Suzuki−Miyaura cross-coupling (MacMillan). In addition to the Suzuki−Miyaura cross-coupling,[9] other Pd-catalyzed methods such as Negishi[10] and Stille[11] reactions have also been used to establish the C16−C18 connection in a series of diazonamide A synthetic studies.

Our approach toward diazonamide A is based on an initial stereoselective assembly of the right-hand heteroaromatic macrocycle **2** by Suzuki cross-coupling of enantiomerically pure hemiaminal bromide (*R*,*R*)-**5** with indolyl boronate **4**, followed by atropodiastereoselective Dieckmann-type cyclization of biaryl **3** (Scheme 1). The Suzuki approach to C16−C18 bond formation is superior to Stille methodology reported earlier because the latter requires elaboration of the expensive enantiomerically pure hemiaminal bromide (*R*,*R*)-**5** to the corresponding stannate.[11] Furthermore, the Stille coupling had used an excess of the stannane for stoichiometric coupling with an isolable palladium intermediate related to **4** (Pd in place of B).

RESULTS AND DISCUSSION

The C16−C18 connection via Suzuki coupling required preparation of the chiral, nonracemic bromide (*R*,*R*)-**5** and N-protected indolyl boronate **4**. The bromide (*R*,*R*)-**5** was obtained from *N*-Alloc-protected enantiomerically pure bicyclic hemiaminal (*R*,*R*)-**6**[12] in a two-step sequence comprising a cleavage of the *N*-Alloc protecting group using Pd(0) catalyst and 1,3-dimethylbarbituric acid **7** as described previously,[11] followed by installation of an *N*-MOM protecting group in the TMS-Cl-mediated reaction of (*R*,*R*)-**8**[13] with paraformaldehyde and MeOH (Scheme 2).[14]

The indolyl boronate subunit **4** for the Suzuki cross-coupling was prepared from a known triflate **15** (Scheme 3). The synthesis of triflate **15** was reported earlier, but this procedure was difficult due to the need to handle methylisocyanide during the formation of the oxazole moiety.[9b] This sequence proved to be especially challenging on a large scale, so an alternative procedure has been developed. Thus, ethyl acetamidoacetate was converted into the Weinreb amide **11** using diethylaluminum activation of *N*,*O*-dimethylhydroxylamine hydrochloride. Next, the acidic proton in the amide functional group of **11** was deprotonated with *i*-PrMgCl to avoid quenching the basic intermediate in the next step. Thus, the resulting magnesiated amide intermediate was reacted with lithiated indole **10**, prepared from 3-bromoindole **9**[9b] by low-temperature lithium−halogen exchange with *t*-BuLi. The resulting ketoamide **12** was transformed into the oxazole **13** using Wipf's cyclodehydration conditions.[15] Subsequent cleavage of the benzyl ether (Pd/C, H_2) and treatment of the resulting phenol **14** with NaH and $PhN(SO_2CF_3)_2$ afforded the triflate **15** in 92% yield.

Next, conversion of triflate **15** to boronate **4** was addressed. The use of bis(pinacolato)diboron $(BPin)_2$ under various

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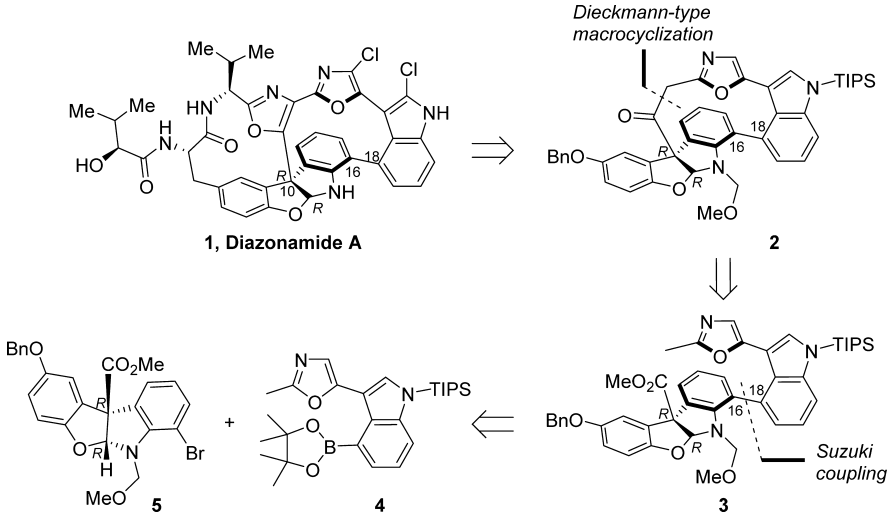
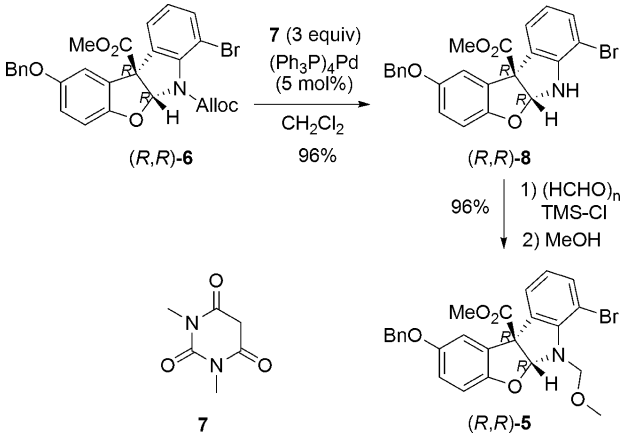
Scheme 1. Retrosynthetic Analysis of Diazonamide A



Scheme 2. Preparation of Hemiaminal (*R*,*R*)-5



conditions ($PdCl_2$(dppf)/KOAc/DMSO,[16] $Pd(Ph_3P)_4$/KOAc/NMP,[17] and $Pd(OAc)_2$/S-Phos/K_3PO_4/dioxane[18]) resulted in poor conversion and different decomposition products such as those derived from the cleavage of *N*-TIPS, hydrolysis of the triflate **15**, or protonolysis of the boronate **4**. It was also found that the yield of the desired boronate **4** depended on the quality of the bis(pinacolato)diboron: even small amounts of the pinacol impurity (5−10 mol %) in the $(BPin)_2$ reagent was sufficient to decrease the conversion of the triflate **15** by 40−60%. In contrast, the use of pinacol borane (PinBH) as an alternative boron source and $Pd(OAc)_2$/DPE-Phos as a catalyst[19] allowed for the conversion of the indolyl triflate **15** into the boronate **4** in reproducible 91% yield.

With both subunits for the cross-coupling in hand, a preliminary screening of the Suzuki−Miyaura reaction conditions was performed using the boronate **4** and 7-bromindoline as a model bromide. 1,4-Dioxane was found to be the best solvent, and K_2CO_3 and K_3PO_4 were the most suitable bases which did not affect the *N*-TIPS protecting group in the boronate **4**. Importantly, rigorous removal of moisture and oxygen traces was found to be critical for the success of the cross-coupling.[20] After the best base was established, screening of Pd catalysts was performed using the hemiaminal bromide (*R*,*R*)-**5** and the boronate **4**. Among various Pd catalysts examined, those formed in situ from $Pd(dba)_2$ and biaryl phosphine ligands were least efficient, affording debrominated (*R*,*R*)-**5** and the protodeboronated derivative of **4** as major products (entries 1 and 2, Table 1). Substantial amounts of the debrominated (*R*,*R*)-**5** were also formed using $Pd(PPh_3)_4$ and

Scheme 3. Synthesis of Boronate 4

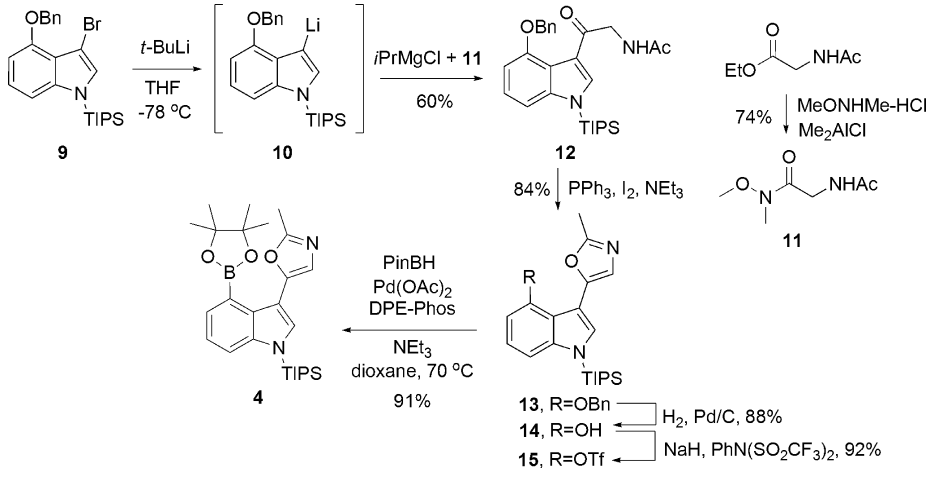


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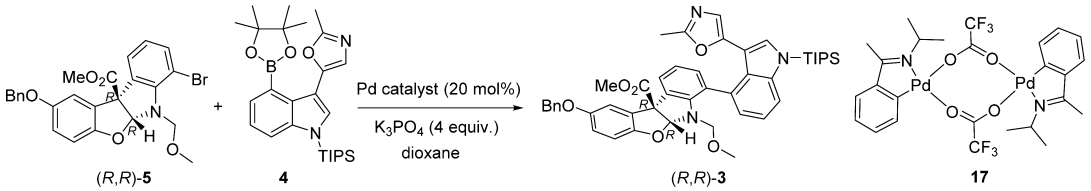
Table 1. Catalyst Screening for Suzuki–Miyaura Cross-Coupling Reaction



(*R*,*R*)-**5** **4** (*R*,*R*)-**3** **17**

entry	catalyst, conditions[a]	conversion of (*R*,*R*)-**5**, %[b]	(*R*,*R*)-**3**, %[b]	major side product[c]
1	$Pd(dba)_2$, S-Phos (Pd/L = 1:2), 100 °C, 40 h	51	10	A, B
2	$Pd(dba)_2$, X-Phos (Pd/L = 1:2), 100 °C, 40 h	56	4	A, B
3	$Pd(PPh_3)_4$, 100 °C, 120 h	68	63	A
4	$Pd(dppf)Cl_2 x CH_2Cl_2$, 100 °C, 40 h	76	50	A
5	$(P\text{-}tBu_3)_2Pd$, 100 °C, 20 h	40	11	B
6	$Pd_2(dba)_3$, PCy_3 (Pd/L = 1:2), 100 °C, 40 h[d]	44	20	A
7	$(PCy_3)_2Pd$,[f] 120 °C, 20 h	96	81 (82)[e]	
8	$(PCy_3)_2Pd$,[g] 120 °C, 20 h	80	55 (47)[e]	
9	$(PCy_3)_2Pd$,[h] 120 °C, 20 h	42	20	A
10	$(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**), 120 °C, 20 h	99	83 (81)[i]	
11[j]	$(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**), 110 °C, 38 h	99	(76)[e]	
12[j]	palladacycle **17**, 110 °C, 20 h	58	57	
13[j]	$(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**), metallic Hg,[k] 110 °C, 18 h	60	21	

[a]With 20 mol % of palladium catalyst used in all experiments. [b]Determined by HPLC using three-point calibration and 4-methylbenzonitrile as an internal standard; reactions performed on 0.1 mmol scale. [c]A: debrominated (*R*,*R*)-**5**. B: Protodeboronated **4**. [d]Use of 1.2 equiv of PCy_3 per Pd afforded increased amounts (38%) of debrominated (*R*,*R*)-**5** (at 60% conversion). [e]In parentheses, isolated yield of >95% pure (*R*,*R*)-**3** (HPLC assay), 0.4 mmol scale. [f]Batch of the catalyst which was handled under air. [g]Fresh, unopened batch of catalyst as received from vendor. [h]Catalyst synthesized from $(COD)PdBr_2$ (see ref 22a) and handled in a glovebox. [i]In parentheses, isolated yields of >92% pure (*R*,*R*)-**3** (HPLC assay), 0.4 mmol scale. [j]Reaction was performed in toluene. [k]Metallic Hg was added 30 min after the beginning of the cross-coupling reaction.

$Pd(dppf)Cl_2 x CH_2Cl_2$ as catalysts (entries 3 and 4). $(P\text{-}tBu_3)_2Pd$[21] afforded poor conversion and delivered a considerable amount of the protodeboronated indole **4** (entry 5). In sharp contrast, $(PCy_3)_2Pd$ catalyzed the formation of the desired biaryl **3** in excellent yields (entry 7), but these results proved difficult to reproduce. A catalyst formed in situ from $Pd_2(dba)_3$ and PCy_3 (Pd/L = 1:2) was far less efficient (entry 6).

Importantly, inconsistent yields of the biaryl **3** were obtained using different batches of the $(PCy_3)_2Pd$ catalyst. Thus, a 2-fold decrease in yield was observed using a freshly opened batch of the commercial $(PCy_3)_2Pd$ catalyst compared to a batch that was handled under air (entry 8 vs entry 7). Comparison of ^{31}P NMR spectra (in C_6D_6) of the two $(PCy_3)_2Pd$ samples showed that both possessed two signals: one at 39.0 ppm (assigned to $(PCy_3)_2Pd$ species)[22] and another signal at 45.0 ppm. The latter signal was tentatively assigned to a dioxygen complex $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**) that could form upon exposure of solid $(PCy_3)_2Pd$ to air.[23] The ratio of the ^{31}P NMR signals was different in all of the commercial $(PCy_3)_2Pd$ batches. Thus, the more active Pd catalyst (entry 7; $(PCy_3)_2Pd$, exposed to air) displayed a major signal at 45.0 ppm corresponding to the dioxygen complex $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**), whereas the ^{31}P NMR spectrum of the less active Pd catalyst batch (entry 8) showed the major signal at 39.0 ppm, corresponding to the $(PCy_3)_2Pd$ species. To determine if the catalytic activity is associated with Pd–dioxygen complex **16**, pure $(PCy_3)_2Pd$ was synthesized from $(COD)PdBr_2$[22a] under oxygen-free conditions using the Schlenk technique. The ^{31}P NMR spectrum of the synthesized $(PCy_3)_2Pd$ catalyst did not contain the signal at 45.0 ppm, confirming the absence of $(PCy_3)_2Pd(\eta^2\text{-}O_2)$. This relatively pure catalyst turned out to be the least efficient among all tested $(PCy_3)_2Pd$ batches (entry 9), confirming that the Pd–dioxygen complex **16** apparently is an actual catalyst in the cross-coupling between the bromide (*R*,*R*)-**5** and the boronate **4**. Finally, pure $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**) was synthesized by suspending the white crystalline $(PCy_3)_2Pd$ in precooled Et_2O (at −20 °C) and stirring for 10 min under air to afford an aquamarine solid which showed a single peak in the ^{31}P NMR spectrum at 45.0 ppm. The structure of the Pd–dioxygen complex **16** was confirmed by X-ray crystallographic analysis (Figure 1).[24,25]

As anticipated from the control studies described above, but contrary to our initial expectations and intuition, an experiment using $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**) resulted in complete conversion of (*R*,*R*)-**5**, affording the biaryl (*R*,*R*)-**3** in 81% yield (entry 10).

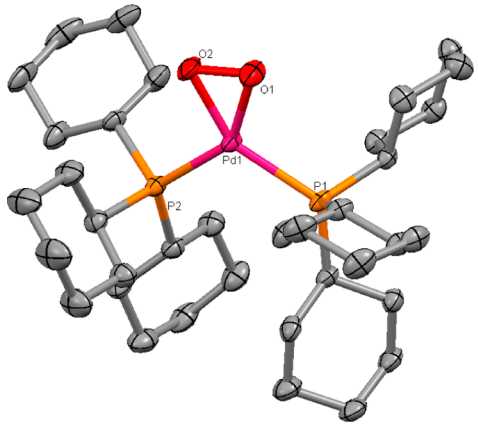


Figure 1. X-ray crystal structure of $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**) (ellipsoids at 50% probability) with hydrogen atoms omitted for clarity. Selected bond distances (Å) and angles (deg): O1–O2, 1.443(6); Pd–O1, 2.015(4); Pd–O2, 2.021(4); Pd–P1, 2.301(1); Pd–P2, 2.295(1); P1–Pd–P2, 111.75(5). See the Supporting Information for details.

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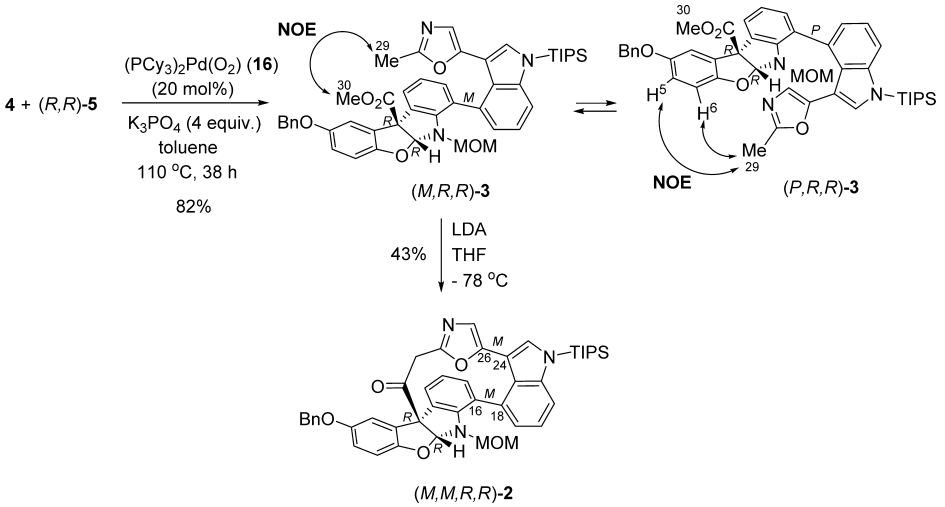
Scheme 4. Synthesis of Macrocycle (*M,M,R,R*)-2



Dioxane and toluene were equally efficient as solvents (entries 10 and 11); however, better reproducibility of the cross-coupling yields was observed in toluene. Therefore, toluene was used as the solvent in all subsequent cross-coupling experiments. The Suzuki reaction in THF and DME delivered the *N*-TIPS-deprotected biaryl **3** as the major product (50−60%) together with the debrominated (*R,R*)-**5** (30%). To the best of our knowledge, this is the first example of the Suzuki−Miyaura cross-coupling that is catalyzed by a Pd−dioxygen complex.[26]

The superiority of $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**) as the catalyst compared to $(PCy_3)_2Pd$ species is intriguing given a low thermal stability of the Pd−dioxygen complex **16**.[24a] Thus, 64% of $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**) was decomposed to $Cy_3P{=}O$ (57%) and $(PCy_3)_2Pd$ species (7%) after 15 min at 60 °C in dioxane-d_8, as evidenced by ^{31}P spectroscopy. Furthermore, the solution turned brown, and formation of Pd black was also observed. Poor thermal stability of the Pd−dioxygen complex **16** puts in question its involvement in the catalytic cycle of the cross-coupling between (*R,R*)-**5** and **4**, as the latter requires prolonged heating at 110−120 °C to go to completion (entries 10 and 11). On the other hand, the observed formation of black colloidal palladium upon thermal degradation of **16** suggests an involvement of heterogeneous Pd species in the catalytic cycle of the Suzuki cross-coupling. It has been demonstrated that heterogeneous Pd species are true catalysts in the Suzuki−Miyaura reaction[27] and that certain palladacycles such as **17**[28] produce catalytically active heterogeneous Pd species at elevated temperatures used in cross-coupling reactions.[29] The imine-based palladacycle **17** was tested as the catalyst in the cross-coupling between (*R,R*)-**5** and **4** under the optimal conditions (entry 12, Table 1). The biaryl (*R,R*)-**3** was formed in 57% yield, so the Pd species formed from **17** can indeed catalyze the cross-coupling in the absence of stabilizing phosphine ligands. Further evidence for a possible involvement of heterogeneous Pd species was obtained in a "mercury drop" test.[30] Accordingly, 600 equiv of metallic Hg (with respect to the Pd−dioxygen complex **16**) was added to the cross-coupling reaction mixture 30 min after the reaction had been initiated (entry 13). Within the 30 min (before the mercury drop was added), the biaryl (*R,R*)-**3** had already been formed in 20% yield (39% conversion). After the Hg addition, the heating at 110 °C was continued for another 18 h. Importantly, the yield of the biaryl (*R,R*)-**3** remained virtually unchanged (21% at 60% conversion) after the prolonged heating. Apparently, the added mercury inhibited the cross-coupling catalyzed by Pd−dioxygen complex **16**, presumably by amalgamation of heterogeneous Pd species. Thus, we regard the catalysis by the heterogeneous Pd species formed in situ to be plausible;[31] however, operation of a homogeneous pathway leading to the formation of biaryl (*R,R*)-**3** cannot be ruled out.[32]

The ^1H NMR spectrum of the biaryl (*R,R*)-**3** in benzene-d_6 at 20 °C displayed two sets of signals in a 3:2 ratio corresponding to a mixture of two atropisomers. The ratio was measured by integration of signals corresponding to the C27 oxazole proton (δ 6.53 and 6.04 ppm), C30 ester protons (δ 3.44 and 3.13 ppm), and C29 methyl group (δ 2.02 and 1.76 ppm). The structures of the atropisomers were assigned on the basis of NOE experiment. Thus, a medium intensity NOE cross-peak was observed between the C29 methyl group and the C30 ester protons of the major atropisomer, whereas weak intensity NOE interactions between C29 methyl group and aromatic C5 and C6 protons were observed for the minor atropisomer (Scheme 4). Consequently, the major and minor atropisomers of the biaryl (*R,R*)-**3** were assigned *M*- and *P*-configurations around the C16−C18 bond, respectively. The two atropisomers underwent interconversion at room temperature, and the free energy of activation and rate constants for the atropisomerization of (*R,R*)-**3** were determined at 25 °C in benzene-d_6 by NMR methods.[33] The barrier to rotation around the C16−C18 bond was measured to be 20.0 kcal/mol, which corresponds to a half-life of ca. 58 s for atropisomerization. However, at temperatures below −20 °C, the interconversion between *M*- and *P*-atropisomers of (*R,R*)-**3** in THF-d_8 was slow on the NMR time scale.

The *M*/*P* = 3:2 equilibrium mixture of atropisomers was employed in the subsequent Dieckmann-type macrocyclization at −78 °C by using lithium diisopropylamide (LDA) as the base. The low temperature was critical for the success of the macrocyclization because at higher temperatures (such as −40 °C) the decomposition of the lithiated (*R,R*)-**3** became a major reaction. Importantly, the macrocyclization at −78 °C apparently proceeds below the threshold for atropisomer interconversion. This implies that only the major atropisomer (*M,R,R*)-**3** may be transformed into the macrocycle (*M,M,R,R*)-**2** with ca. 60% theoretical yield. In fact, the target macrocycle (*M,M,R,R*)-**2** was formed in 43% yield within 10 min, and

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prolonged reaction times (30 min) did not improve the yield. The unreacted biaryl (*R*,*R*)-**3** was also recovered as a *M*/*P* = 3:2 mixture of atropisomers (40% yield, 83% material balance). Evidently, the unreacted atropisomer (*P*,*R*,*R*)-**3** had re-equilibrated during workup to the *M*/*P* = 3:2 equilibrium mixture. This allows for the reuse of the recovered material in the macrocyclization.

CONCLUSIONS

Atropodiastereoselective Dieckmann-type cyclization provides an access to the macrocyclic core of diazonamide A in enantiomerically pure form. The diastereoselectivity of the macrocyclization was controlled by the (*R*)-stereogenic center at C10 of the rigid tetracyclic hemiaminal moiety. Notably, *M*-configuration around both C16−C18 and C24−C26 biaryl bonds of the macrocycle was simultaneously established in the cyclization step. The Dieckmann-type cyclization proceeded below the threshold for interconversion of atropisomers around the C16−C18 biaryl bond in the starting biaryl (*R*,*R*)-**3**. Therefore, only the *M*-atropisomer underwent the ring closure, whereas the *P*-atropisomer did not react. However, the unreacted *P*-atropisomer equilibrated back to the starting 3:2 *M*/*P* mixture during the workup, and hence, the recovered biaryl (*R*,*R*)-**3** can be reused in the macrocyclization. The biaryl (*R*,*R*)-**3** was prepared in the Suzuki−Miyaura cross-coupling between the chiral, nonracemic tetracyclic hemiaminal bromide and indolyl boronate. Unexpectedly, palladium−dioxygen complex $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**) was found to be the most efficient catalyst in the Suzuki−Miyaura reaction. Suzuki−Miyaura coupling has been used in other diazonamide studies, but only the MacMillan synthesis included an intact unprotected aminal subunit having the correct functionality.[7] Further elaboration of the enantiomerically pure macrocyclic core of diazonamide A will be reported in due course.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all chemicals were used as obtained from commercial sources and all reactions were performed under nitrogen or argon atmosphere in glassware dried in an oven (120 °C) and cooled under a stream of nitrogen or argon. Toluene, tetrahydrofuran (THF), and 1,4-dioxane were distilled from sodium/benzophenone prior the use. Dry CH_2Cl_2 and Et_2O were obtained by passing commercially available anhydrous solvents through activated alumina columns. Commercially available anhydrous K_3PO_4 was heated at 250 °C for 3 h and stored in a glovebox under argon atmosphere.

Analytical thin-layer chromatography (TLC) was performed on precoated silica gel F-254 plates. Flash chromatography was performed using Davisil LC60A 35−70 μm silica gel. High-resolution mass spectra were recorded on a mass spectrometer with a time-of-flight (TOF) mass analyzer. Nuclear magnetic resonance spectra were recorded on NMR spectrometers at the following frequencies: ^1H, 400 or 600 MHz; $^{13}C\{^1H\}$, 101 or 126 MHz; ^{31}P, 162 MHz. Chemical shifts were referenced to Me_4Si as an internal reference or to residual solvent peaks. Signals in ^{31}P were referenced to H_3PO_4 as an external standard.

2-Acetylamino-*N*-methoxy-*N*-methylacetamide (11). To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (9.76 g, 100 mmol) in CH_2Cl_2 (400 mL) was added Me_2AlCl (1.0 M in hexanes, 100 mL, 100 mmol) at 0 °C.[34] After being stirred at room temperature for 30 min, ethyl acetamidoacetate (7.26 g, 50.0 mmol) was added, and stirring at room temperature was continued for 2 h. The reaction mixture was then treated with EtOAc (50 mL) and MeOH (50 mL) and stirred for 10 min. To this solution was added SiO_2 (50 g), and the suspension was concentrated under reduced pressure. The resulting crude solid was loaded onto SiO_2 and eluted with EtOAc, followed by 10% MeOH in EtOAc to afford **11** (5.90 g, 74% yield) as a white solid: analytical TLC on silica gel, EtOAc, R_f = 0.16; pure material was obtained by crystallization from CH_2Cl_2/hexanes; mp 96−97 °C; IR (film, cm^{-1}) 3278 (N−H), 1676 (C═O), 1654 (C═O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 6.36 (1H, br s), 4.18 (2H, d, *J* = 4.0 Hz), 3.71 (3H, s), 3.21 (3H, s), 2.04 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 170.3, 169.9, 61.7, 41.0, 32.5, 23.2. Anal. Calcd for $C_6H_{12}N_2O_3$: C, 44.99; H, 7.55; N, 17.49. Found: C, 45.00; H, 7.57; N, 17.50.

***N*-(2-(4-(Benzyloxy)-1-(triisopropylsilyl)-1*H*-indol-3-yl)-2-oxoethyl)acetamide (12).** A solution of 2-acetylamino-*N*-methyl-*N*-methoxyacetamide (**11**) (1.20 g, 7.50 mmol) in anhydrous THF (75 mL) was cooled to −15 °C under nitrogen atmosphere, and *i*-PrMgCl (2.0 M solution in THF, 5.60 mL, 11.2 mmol) was slowly added. The resulting light gray suspension was stirred for 30 min at −15 °C under nitrogen atmosphere.[35] In a separate flask, to a cooled solution of 4-benzyloxy-3-bromo-1-triisopropylsilylindole (**9**)[9b] (3.44 g, 7.5 mmol) in anhydrous THF (75 mL) was slowly added *t*-BuLi (1.6 M solution in pentane, 9.4 mL, 15 mmol) at −78 °C under nitrogen atmosphere at a rate to maintain the internal temperature below −70 °C. The resulting orange solution was stirred for 15 min at −78 °C, whereupon the color changed to carmine red. The solution of the lithiated indole was then transferred using a metal cannula to the light gray suspension of magnesium amide from above, which was cooled to −15 °C. The resulting pale yellow slurry was warmed to room temperature and left to stir for 20 h, whereupon a clear pale yellow solution was formed. The reaction was quenched with saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (3 × 50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL), and the combined aqueous layers were extracted with EtOAc (150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was loaded on SiO_2, which had been pretreated with 0.1% triethylamine in hexanes. Elution with 50% EtOAc and 0.1% NEt_3 in hexanes afforded **12** (2.16 g, 60%) as a white solid: analytical TLC on silica gel, 1:1 hexanes/EtOAc, R_f = 0.60; pure material was obtained by crystallization from Et_2O; mp 137−138 °C; IR (film, cm^{-1}) 3364 (N−H), 1674 (C═O), 1650 (C═O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.84 (1H, s), 7.54 (2H, d, *J* = 7.6 Hz), 7.37 (2H, t, *J* = 7.9 Hz), 7.32−7.27 (1H, m), 7.14−7.08 (2H, m), 6.73 (1H, dd, *J* = 6.4, 2.1 Hz), 6.46 (1H, br s), 5.27 (2H, s), 4.74 (2H, d, *J* = 4.4 Hz), 2.01 (3H, s), 1.69 (3H, septet), 1.13 (18H, d, *J* = 7.4 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 191.4, 170.0, 152.6, 143.5, 137.8, 136.9, 128.5, 127.99, 127.95, 123.8, 118.8, 117.6, 107.8, 104.4, 70.5, 49.2, 23.0, 17.9, 12.6. Anal. Calcd for $C_{28}H_{38}N_2O_3Si$: C, 70.25; H, 8.00; N, 5.85. Found: C, 70.24; H, 8.00; N, 5.80.

5-(4-(Benzyloxy)-1-(triisopropylsilyl)-1*H*-indol-3-yl)-2-methyloxazole (13). To a stirred solution of ketone **12** (1.20 g, 2.51 mmol) in anhydrous CH_2Cl_2 (100 mL) under nitrogen atmosphere was added PPh_3 (3.17 g, 12.05 mmol), followed by I_2 (3.06 g, 12.05 mmol) and NEt_3 (3.50 mL, 25.10 mmol). The reaction mixture was stirred at room temperature for 2 h, diluted with EtOAc (100 mL), and washed with saturated aqueous $Na_2S_2O_3$ solution (2 × 100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous washings were combined and extracted with EtOAc (100 mL). Organic extracts were combined and dried over Na_2SO_4. Column chromatography on silica gel using gradient elution from 6% EtOAc in hexanes to 20% EtOAc in hexanes afforded **13** as a yellow foam (972 mg, 84% yield): analytical TLC on silica gel, 2:5 EtOAc/hexanes, R_f = 0.33; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.43−7.29 (6H, m), 7.14−7.04 (3H, m), 6.64 (1H, d, *J* = 7.6 Hz), 5.17 (2H, s), 2.34 (3H, s), 1.70 (3H, septet), 1,15 (18H, d, *J* = 7.8); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.4, 153.1, 147.6, 143.4, 136.8, 128.9, 128.7, 128.3, 128.2, 123.4, 123.1, 118.1, 107.9, 107.5, 102.2, 70.5, 18.3, 14.1, 12.9; HRMS-ESI (*m*/*z*) calcd for $C_{28}H_{37}N_2O_2Si$ $[M + H]^+$ 461.2619, found 461.2621.

3-(2-Methyloxazol-5-yl)-1-(triisopropylsilyl)-1*H*-indol-4-ol (14). To a solution of indole **13** (1.97 g, 4.28 mmol) in abs. EtOH (40 mL) was added 10% Pd−C (182 mg, 0.171 mmol, 4 mol %), and H_2 gas was passed through the resulting suspension at room temperature.

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Progress of the hydrogenation was followed by TLC (2:5 EtOAc/hexanes, starting indole **13** R_f = 0.33; product **14** R_f = 0.13). Usually, it required 4−6 h for the hydrogenation to go to completion. In case of incomplete conversion after 6 h, it is recommended to add an additional amount of 10% Pd−C (182 mg, 0.171 mmol, 4 mol %) and continue the hydrogenation. Once the reaction is completed, it was filtered through a plug of Celite. The filter cake was washed with EtOH (120 mL), EtOAc (200 mL), and Et_2O (120 mL). All filtrates were combined and solvents were concentrated (aspirator) to afford **14** as a grayish amorphous material (1.4 g, 88% yield): analytical TLC on silica gel, 1:1 EtOAc/hexanes, R_f = 0.41; IR (film, cm^{-1}) 3143 (O−H); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.38 (1H, s), 7.18 (1H, s), 7.07−7.05 (2H, m), 6.69 (1H, br s), 6.63 (1H, m), 2.54 (3H, s), 1.70 (3H, septet, J = 7.5 Hz), 1.15 (18H, d, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 159.3, 149.6, 147.4, 143.5, 128.6, 123.5, 121.3, 116.4, 106.9, 106.3, 105.4, 18.0, 14.1, 12.7; HRMS-ESI (m/z) calcd for $C_{21}H_{31}N_2O_2Si$ $[M + H]^+$ 371.2149, found 371.2153.

3-(2-Methyloxazol-5-yl)-1-(triisopropylsilyl)-1*H*-indol-4-yltrifluoromethanesulfonate (15). A dispersion of NaH in mineral oil (60%, 290 mg, 1.23 mmol) was added portionwise to a solution of 4-hydroxyindole **14** (1.30 g, 3.51 mmol) in anhydrous THF (40 mL) at 0 °C under atmosphere of nitrogen. The resulting suspension was stirred at ambient temperature for 2 h until gas evolution ceased. Then a solution of *N*-phenyl-bis(trifluoromethanesulfonimide) (2.19 g, 6.14 mmol) in anhydrous THF (10 mL) was added in one portion, and the reaction mixture was stirred for 1 h at room temperature, whereupon it was poured into aqueous $NaHCO_3$ solution (100 mL; aqueous saturated $NaHCO_3$ solution was diluted 1:1 with water). Aqueous layer was extracted with Et_2O (2 × 100 mL), and combined organic extracts were washed with H_2O (130 mL) and brine (150 mL) and dried over Na_2SO_4. Column chromatography (100 mL silica gel, column i.d. 30 mm) using gradient elution from 10% EtOAc in hexanes to 20% EtOAc in hexanes afforded **15** as a yellowish amorphous solid (1.61 g, 92% yield): analytical TLC on silica gel, 2:5 EtOAc/hexanes, R_f = 0.52; IR (film, cm^{-1}) 1221 (S═O), 1213 (S═O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.51 (1H, d, J = 8.2 Hz), 7.43 (1H, s), 7.19 (1H, t, J = 8.1 Hz), 7.13 (1H, d, J = 8.1 Hz), 7.04 (1H, s), 2.52 (3H, s), 1.70 (3H, septet, J = 7.5 Hz), 1.15 (18 H, d, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 161.1, 145.0, 143.8, 142.7, 132.6, 123.9, 122.2, 121.0, 120.2, 114.3, 112.8, 105.4, 18.0, 14.0, 12.7; HRMS-ESI (m/z) calcd for $C_{22}H_{30}F_3N_2O_4SSi$ $[M + H]^+$ 503.1642, found 503.1651.

2-Methyl-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-1*H*-indol-3-yl)oxazole (4). To a mixture of $Pd(OAc)_2$ (13.0 mg, 0.057 mmol, 1.5 mol %), DPE-Phos (61 mg, 0.114 mmol, 3 mol %), and triflate **15** (1.70 g, 3.38 mmol) in anhydrous dioxane (30 mL) under nitrogen atmosphere was added NEt_3 (1.6 mL, 11.43 mmol), followed by pinacolborane (830 μL, 5.72 mmol). The resulting yellow solution was heated at 80 °C for 1 h in a sealed vessel under nitrogen atmosphere, cooled to ambient temperature, poured into water (150 mL), and extracted with EtOAc (2 × 150 mL). The organic extracts were combined and washed with brine, dried on Na_2SO_4, filtered, and concentrated. Column chromatography (200 mL of silica gel, column i.d. 45 mm) using gradient elution from 10% EtOAc in hexanes to 50% EtOAc in hexanes afforded **4** as a yellowish oil (1.48 g, 91%) that crystallized upon standing: analytical TLC on silica gel, 1:1 Et_2O/hexanes, R_f = 0.20; pure material was obtained by crystallization from CH_2Cl_2/hexanes, mp 97−98 °C; IR (film, cm^{-1}) 1363 (B−O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.61 (2H, dt, J = 8.5, 0.8 Hz), 7.34 (1H, s), 7.17 (1H, m), 6.92 (1H, s), 2.50 (3H, s), 1.68 (3H, septet, J = 7.6 Hz), 1.21 (12H, s), 1.13 (18H, d, J = 7.7 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 160.1, 147.1, 140.7, 134.2, 133.1, 129.1, 124.3, 121.4, 116.8, 107.7, 83.3, 29.8, 24.7, 18.0, 14.5, 12.8. Anal. Calcd for $C_{27}H_{41}N_2O_3SiB$: C, 67.49; H, 8.60; N, 5.83. Found: C, 67.23; H, 8.79; N, 5.65.

Methyl (5a*R*,10b*R*)-2-(benzyloxy)-7-bromo-5a,6-dihydro-10b*H*-benzofuro[2,3-*b*]indole-10b-carboxylate (*R*,*R*-8). 1,3-Dimethylbarbituric acid (7) (437 mg, 2.80 mmol) and $Pd(PPh_3)_4$ (54 mg, 0.047 mmol, 5 mol %) were added to a cooled (0 °C) solution of bromide (*R*,*R*)-**6**[12] (500 mg, 0.932 mmol) in anhydrous CH_2Cl_2 (15 mL). The reaction mixture was stirred at 0 °C for 15−20 min, and the color of the solution turned bright yellow. The reaction was complete at that point. The solution was poured into a 1:1:2 mixture of water, saturated aqueous $NaHCO_3$, and saturated aqueous Na_2CO_3 (50 mL). Layers were separated, and the aqueous layer was extracted with Et_2O (3 × 80 mL). The organic extracts were combined, washed with water (100 mL) and brine, and dried over Na_2SO_4. Column chromatography (50 mL silica gel, column i.d. 30 mm) using gradient elution from 10% EtOAc in hexanes to 30% EtOAc in hexanes afforded (*R*,*R*)-**8** as colorless solid (405 mg, 96% yield): analytical TLC on silica gel, 2:5 EtOAc/hexanes, R_f = 0.58; pure material was obtained by crystallization from CH_2Cl_2/hexanes, mp 183−184 °C; IR (film, cm^{-1}) 1734 (C═O), 1487; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.44−7.30 (6H, m), 7.26 (1H, dd, J = 8.0, 1.0 Hz), 7.22 (1H, d, J = 2.7 Hz), 6.85 (1H, d, J = 2.7 Hz), 6.81 (1H, dd, J = 8.7, 2.7 Hz), 6.75 (1H, d, J = 8.7 Hz), 6.67 (1H, t, J = 7.8 Hz), 5.27 (1H, d, J = 2.4 Hz), 5.01 (2H, s), 3.82 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 169.7, 154.0, 152.7, 146.2, 137.1, 132.0, 128.7, 128.1, 128.1, 127.8, 127.2, 123.3, 121.1, 116.1, 111.9, 110.5, 102.8, 99.2, 71.3, 67.3, 53.4; HRMS-ESI (m/z) calcd for $C_{23}H_{19}BrNO_4$ $[M + H]^+$ 452.0492, found 452.0495; optical rotation $[\alpha]_D^{20}$ −176 (c 0.1, benzene). Anal. Calcd for $C_{23}H_{18}BrNO_4$: C, 61.08; H, 4. 01; N, 3.10. Found: C, 60.61; H, 3.96; N, 2.99.

Methyl (5a*R*,10b*R*)-2-(Benzyloxy)-7-bromo-6-(methoxymethyl)-5a,6-dihydro-10b*H*-benzofuro[2,3-*b*]indole-10b-carboxylate (*R*,*R*-5). An oven-dried pressure tube was charged with hemiaminal bromide (*R*,*R*)-**8** (390 mg, 0.86 mmol) and paraformaldehyde (129 mg, 4.30 mmol) and flushed with nitrogen. Anhydrous DCM (25 mL) was added, and to the resulting suspension was added TMSCl (275 μL, 2.15 mmol). The pressure tube was closed, and the pale yellow suspension was heated for 24 h at 35 °C. After being cooled to ambient temperature, the suspension was transferred dropwise to precooled (0 °C) anhydrous MeOH (15 mL) using a metal cannula. Stirring was continued at room temperature for 15 min, then the reaction mixture was poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 50 mL). The organic extracts were combined, washed with brine, and dried on Na_2SO_4. Column chromatography on silica gel using 10% EtOAc in hexanes as a mobile phase afforded (*R*,*R*)-**5** as an amorphous colorless solid (410 mg, 96% yield): analytical TLC on silica gel, 2:5 EtOAc/hexanes, R_f = 0.50; IR ($CHCl_3$, cm^{-1}) 1738 (C═O), 1488; ^1H NMR (400 MHz, C_6D_6, ppm) δ 7.48 (1 H, dd, J = 7.5, 1.2 Hz), 7.43 (1 H, d, J = 2.7 Hz), 7.25−7.21 (2 H, m), 7.16−7.05 (4 H, m), 7.01 (1 H, s), 6.67 (1 H, d, J = 8.7 Hz), 6.57 (1 H, dd, J = 8.7, 2.7 Hz), 6.39 (1 H, t, J = 7.8 Hz), 5.42 (1 H, d, J = 10.6 Hz), 4.76 (1 H, d, J = 10.6 Hz), 4.65 (2 H, s), 3.13 (3 H, s), 3.11 (3 H, s); $^{13}C\{^1H\}$ NMR (101 MHz, C_6D_6, ppm) δ 169.4, 154.4, 153.1, 144.7, 137.7, 134.90, 132.7, 128.6, 128.2, 128.0, 127.8, 123.9, 122.5, 116.2, 112.5, 110.8, 105.1, 104.3, 79.4, 71.0, 64.5, 55.0, 52.6; HRMS-ESI (m/z) calcd for $C_{25}H_{23}BrNO_5$ $[M + H]^+$ 496.0754, found 496.0764; optical rotation $[\alpha]_D^{20}$ −235 (c 0.33, benzene).

General Procedure for Optimization of the Suzuki Cross-Coupling (Table 1). The hemiaminal bromide (*R*,*R*)-**5** (30 mg, 0.0604 mmol), the indolyl boronate **4** (29 mg, 0.0604 mmol), an oven-dried K_3PO_4 (51 mg, 0.242 mmol), Pd catalyst (20 mol %), and phosphine ligand (if indicated in Table 1) were weighted into an oven-dried pressure vial in a glovebox (argon atmosphere). A solution of 4-cyanotoluene as an internal standard (0.0604 mmol, 1 equiv with respect to the hemiaminal bromide (*R*,*R*)-**5**) in dry degassed dioxane or toluene (2 mL) was added, and the pressure vial was closed. The reaction mixture was heated in an oil bath (for appropriate time and temperature, see Table 1), and progress of the reaction was monitored by reversed-phase HPLC (an aliqot of the reaction mixture was diluted with MeCN, filtered trough a plug of Celite, and submitted to HPLC analysis). Conversion of the starting bromide (*R*,*R*)-**5** and yield of the biaryl product (*R*,*R*)-**3** were determined based on a calibration curve using the internal standard.

Preparation of $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (16). A freshly prepared solid $Pd(PCy_3)_2$ complex[22a] (294 mg, 0.44 mmol) was weighted into a

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round-bottom flask with stir-bar under an argon atmosphere (in a glovebox), closed with a septum, and immersed into an acetone/dry ice cooling bath (−30 °C). Then the flask was opened, and anhydrous precooled (−20 °C) diethyl ether (3 mL) was added. The resulting colorless suspension was stirred under air at −30 °C for 10 min, whereupon the color of the suspension changed to greenish blue. Stirring was stopped, and the supernatant solution was decanted. Another portion of cold Et_2O (1 mL) was added, and the suspension was stirred under air at −30 °C for 2 min, followed with decantation of the supernatant. The addition of Et_2O/stirring sequence was repeated once more, and after the decantation of the supernatant, the cold solid containing a residual diethyl ether was immediately transferred to a rotary evaporator (preventing the solid to warm to room temperature). Careful drying on rotary evaporator (without immersing of the flask into a bath) afforded **16** (279 mg, 91% yield) as aquamarine powder:[36] ^{1}H NMR (400 MHz, C_6D_6, ppm) δ 2.04 (12H, d, J = 12.3 Hz), 1.96−1.86 (6H, m), 1.78−1.58 (30H, m), 1.28−1.16 (18H, m); $^{13}C\{^1H\}$ NMR (101 MHz, C_6D_6, ppm) δ 35.7 (t, J_{C-P} = 7.8 Hz), 30.8, 28.0 (t, J_{C-P} = 5.3 Hz), 26.7; ^{31}P NMR (162 MHz, C_6D_6, ppm) δ 44.96; ^{31}P NMR (162 MHz, dioxane-d_8, ppm) δ 44.84.

Methyl (5a*R*,10b*R*)-2-(Benzyloxy)-6-(methoxymethyl)-7-(3-(2-methyloxazol-5-yl)-1-(triisopropylsilyl)-1*H*-indol-4-yl)-5a,6-dihydro-10b*H*-benzofuro[2,3-*b*]indole-10b-carboxylate (*R*,*R*-3). The hemiaminal bromide (*R*,*R*)-**5** (200 mg, 0.40 mmol), the indolyl boronate **4** (194 mg, 0.40 mmol), $Pd(PCy_3)_2O_2$ (**16**) (54 mg, 20 mol %), and an oven-dried K_3PO_4 (342 mg, 1.61 mmol) were weighted into an oven-dried pressure vial in a glovebox (argon atmosphere). Anhydrous toluene (13 mL; degassed by freeze−pump−thaw technique prior to use) was added, and the reaction mixture was heated in an oil bath at 110 °C for 38 h, then diluted with EtOAc (50 mL) and washed with water (50 mL). The aqueous layer was back-extracted with EtOAc (50 mL). Combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated (rotary evaporator). Column chromatography on silica gel using gradient elution from 10% acetone in hexanes to 30% acetone in hexanes afforded (*R*,*R*)-**3** as a colorless foam (253 mg, 82% yield, Figures 2 and 3): analytical TLC on silica gel, 2:5 EtOAc/hexanes, R_f

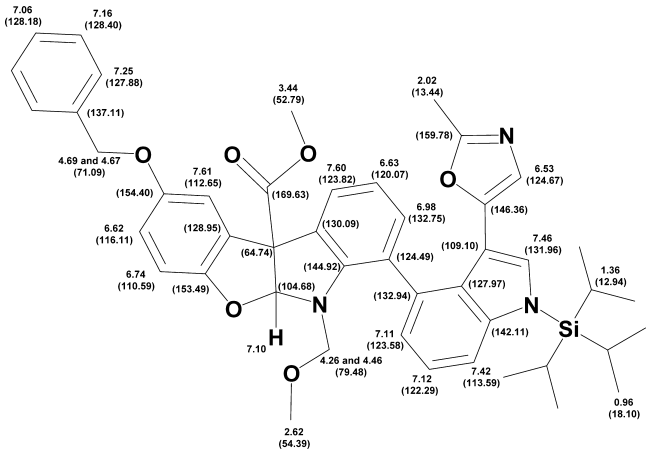

Figure 2. ^{1}H and ^{13}C NMR assignment for the major atropisomer (*M*,*R*,*R*)-**3**.

=0.1−0.50 (tailing); IR (film from $CHCl_3$, cm^{-1}) 1739 (C═O), 1487; ^{1}H NMR (400 MHz, C_6D_6, ppm) δ 7.70 (minor atropisomer, 0.65H, dd, J = 7.6, 1.3 Hz), 7.61 (major atropisomer, 1H, d, J = 2.7 Hz), 7.60 (major, 1H, dd, J = 7.6, 1.3 Hz), 7.59 (minor, 0.65H, d, J = 2.5 Hz), 7.48 (minor, 0.65H, s), 7.47 (minor, 0.65H, dd, J = 8.1, 1.2 Hz), 7.46 (major, 1H, s), 7.42 (major, 1H, dd, J = 6.9, 2.5 Hz), 7.40−7.36 (minor, 1.3H, m), 7.28−7.05 (10.9H, m), 7.10 (major, 1H, s), 7.01 (minor, 0.65H, s), 6.98 (major, 1H, dd, J = 7.6, 1.3 Hz), 6.80 (minor, 0.65H, t, J = 7.6 Hz), 6.76 (minor, 0.65H, dd, J = 8.8, 2.5 Hz), 6.74 (major, 1H, d, J = 8.8 Hz), 6.73 (minor, 0.65H, dd, J = 8.6, 0.5 Hz), 6.63 (major, 1H, t, J = 7.6 Hz), 6.62 (major, 1H, dd, J = 8.8, 2.7 Hz),

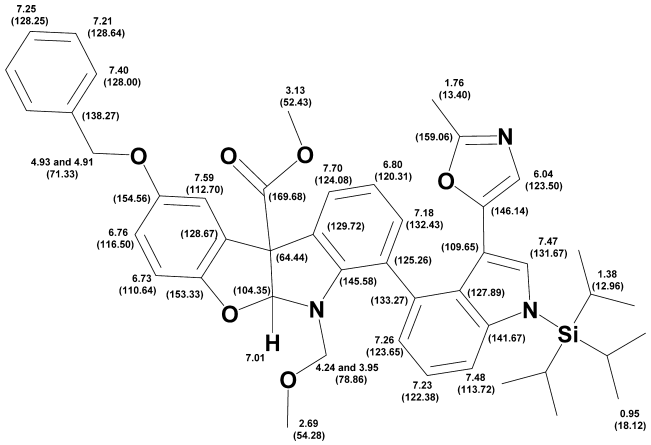

Figure 3. ^{1}H and ^{13}C NMR assignment for the minor atropisomer (*P*,*R*,*R*)-**3**.

6.53 (major, 1H, s), 6.04 (minor, 0.65H, s), 4.93, 4.91 (minor, 1.3H, ABq, J_{AB} = 12.2 Hz), 4.69, 4.67 (major, 2H, ABq, J_{AB} = 12.1 Hz) 4.46 (major, 1H, d, J = 9.9 Hz), 4.26 (major, 1H, d, J = 9.9 Hz), 4.24 (minor, 0.65H, d, J = 9.9 Hz), 3.95 (minor, 0.65H, d, J = 9.9 Hz), 3.44 (major, 3H, s), 3.13 (minor, 1.95H, s), 2.69 (minor, 1.95H, s), 2.62 (major, 3H, s), 2.02 (major, 3H, s), 1.76 (minor, 1.95H, s), 1.44−1.31 (4.95H, m), 0.99−0.93 (29.7H, m); $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6, ppm) δ 169.68, 169.63, 159.78, 159.06, 154.58, 154.40, 153.49, 153.33, 146.36, 146.14, 145.58, 144.92, 142.11, 141.67, 138.27, 137.11, 133.27, 132.94, 132.75, 132.43, 131.96, 131.67, 130.09, 129.72, 128.95, 128.67, 128.64, 128.40, 128.25 (overlapping with residual solvent signal), 128.18, 128.00 (overlapping with residual solvent signal), 127.97, 127.89, 127.88, 125.26, 124.67, 124.49, 124.08, 123.82, 123.65, 123.58, 123.50, 122.38, 122.29, 120.31, 120.07, 116.50, 116.11, 113.72, 113.59, 112.70, 112.65, 110.64, 110.59, 109.65, 109.10, 104.68, 104.35, 79.48, 78.86, 71.33, 71.09, 64.74, 64.44, 54.39, 54.28, 52.79, 52.43, 18.12, 18.10, 13.44, 13.40, 12.96, 12.94; HRMS-ESI (m/z) calcd for $C_{46}H_{52}N_3O_6Si$ $[M + H]^+$ 770.3620, found 770.3615; optical rotation $[\alpha]_D^{20}$ −130 (c 0.35, benzene).

Macrocycle (*M*,*M*,*R*,*R*)-2. A solution of the biaryl (*R*,*R*)-**3** (50 mg, 0.065 mmol) in anhydrous THF (13 mL) was cooled to −78 °C under argon atmosphere, and LDA (0.30 M solution in THF, 0.54 mL, 0.163 mmol) was added in one portion. The reaction mixture was stirred at −78 °C for 10 min, whereupon the clear colorless solution became yellow. At this point, glacial AcOH (0.125 mL) was added, and the resulting colorless solution was allowed to warm to room temperature. The reaction mixture was poured into aqueous 5% $NaHCO_3$ solution (30 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried on $MgSO_4$ and concentrated. Purification of the residue by preparative HPLC (Grom-Sil Si NP-2, 5 μM, 150 × 20 mm) using gradient elution from 0% EtOAc in hexanes to 60% EtOAc in hexanes provided 20 mg (40% recovery) of the starting biaryl (*R*,*R*)-**3** and macrocycle (*M*,*M*,*R*,*R*)-**2** (21 mg, 43% yield) as a pale yellow foam: analytical TLC on silica gel, 1:1 EtOAc/hexanes, R_f = 0.75; IR (film from $CHCl_3$, cm^{-1}) 1714 (C═O), 1485; ^{1}H NMR (600 MHz, C_6D_6, ppm) δ 7.76−7.74 (1H, m), 7.44 (1H, dd, J = 7.0, 2.3 Hz), 7.30−7.25 (2H, m), 7.25−7.21 (2H, m), 7.18 (1H, s), 7.15−7.13 (2H, m), 7.10−7.07 (1H, m), 7.04−7.01 (1H, m), 6.73−6.70 (3H, m), 6.60 (2H, d, J = 9.5 Hz), 6.46 (1H, t, J = 7.5 Hz), 4.80, 4.75 (2H, ABq, J = 11.7 Hz), 4.62 (1H, d, J = 10.3 Hz), 4.31 (1H, d, J = 10.3 Hz), 3.80 (1H, d, J = 14.4 Hz), 3.43 (1H, d, J = 14.4 Hz), 2.75 (3H, s), 1.38−1.29 (3H, m), 0.95 (18H, dd, J = 7.5, 1.0 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, C_6D_6, ppm) δ 197.4, 156.0, 154.5, 153.0, 146.1, 145.5, 140.9, 138.0, 133.4, 133.1, 133.0, 132.0, 128.6, 128.5, 128.4, 128.2, 128.0, 127.4, 123.1, 122.9, 122.5, 121.4, 119.3, 116.3, 114.0, 113.8, 110.1, 107.3, 102.3, 77.9, 71.0, 54.7, 41.7, 18.0, 12.9; HRMS-ESI (m/z) calcd for $C_{45}H_{48}N_3O_5Si$ $[M + H]^+$ 738.3358, found 738.3346; optical rotation $[\alpha]_D^{20}$ −286 (c 1.30, EtOAc).

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, and ^{31}P NMR spectra, X-ray crystallographic data for Pd complex **16** (CIF), Pd particle size measurements, and TEM images. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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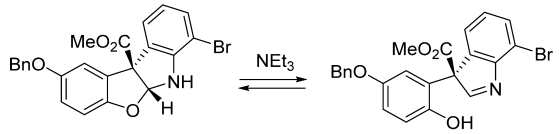

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