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Enantioselective Total Syntheses of (+)-Arborescidine A, (−)-Arborescidine B, and (−)-Arborescidine C

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Described are the first enantioselective total syntheses of (+)-arborescidine A ((+)-**1**), (−)-arborescidine B ((−)-**2**), and (−)-arborescidine C ((−)-**3**), via routes that proceeded in five steps and 50% overall yield, eight steps and 61% overall yield, and nine steps and 51% overall yield, respectively, from 6-bromotryptamine (**7**). The syntheses feature the use of the Noyori catalytic asymmetric hydrogen-transfer reaction to introduce chirality in dihydro-β-carbolines **6** and **8**. On the basis of an ample precedent from Noyori's work, the reduction produces dihydro-β-carbolines, and ultimately the natural products, possessing the *R* absolute configuration. The synthetic arborescidines displayed optical rotations that were opposite in sign those of the natural products, thereby supporting the *S* configuration for natural arborescidines A (**1**) and B (**2**) and the (3*S*,17*S*) configuration for natural arborescidine C (**3**). Our results are in agreement with the initial stereochemical assignment by Païs and co-workers, and are counter to their recently revised assignment.

Introduction

A wide variety of biologically active 6-bromoindole derivatives have been isolated from marine invertebrates, such as sponges, coelenterates, and tunicates. These secondary metabolites are believed to function as chemical defense agents against parasites.[1] In 1993, Païs and co-workers isolated four new brominated alkaloids of the tetrahydro-β-carboline family from the marine tunicate *Pseudodistoma arborescens* and characterized them as arborescidine A (**1**), arborescidine B (**2**), arborescidine C (**3**), and arborescidine D—a diastereoisomer of **3** that possesses the opposite configuration at C-17 (Figure 1).[2] The absolute stereochemistry of **1** was initially suggested to be *S* on the basis of circular dichroism studies by Païs and co-workers. Assuming a common biosynthesis for all four compounds, the same C-3 configuration was also tentatively assigned to arborescidines B−D. However, recent X-ray crystallography studies using the anomalous dispersion of the bromine atom have resulted in the assignment of arborescidine C to be changed to 3*R*,17*R*.[3]

Inspired in part by this controversy, we undertook the stereoselective synthesis of **1**−**3**. In 1998, Koomen and co-workers reported a racemic approach to these alkaloids.[4] We envisaged efficient, enantiocontrolled syntheses of these alkaloids by taking advantage of the Noyori asymmetric hydrogen-transfer reaction of appropriately functionalized β-carboline derivatives.[5]

Results

Structurally, the arborescidines comprise a tetracyclic framework featuring a common octahydropyrido[2,1-*a*]-β-carboline core. The retrosynthetic analysis for the basic framework of arborescidines A−C is depicted in Figure 1 and features the Noyori asymmetric hydrogen-transfer reaction (**6** to **5** and **8** to **9**) as a key step. Although demonstrated as a useful synthetic method, this asymmetric reduction remains to be fully explored in the arena of total synthesis of alkaloid natural products.[6]

The ubiquitous nature of the indole framework has stimulated the development of numerous methods for the

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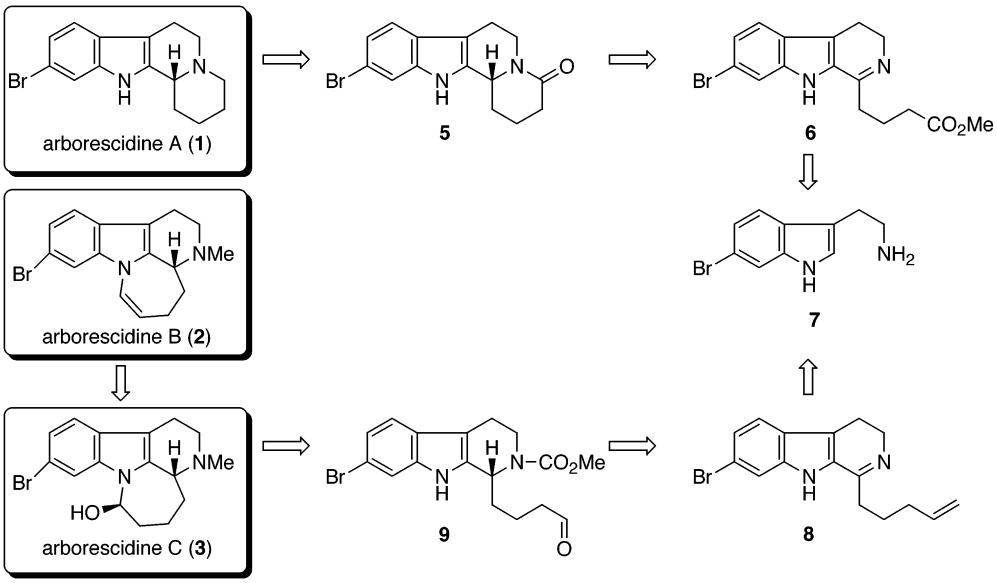
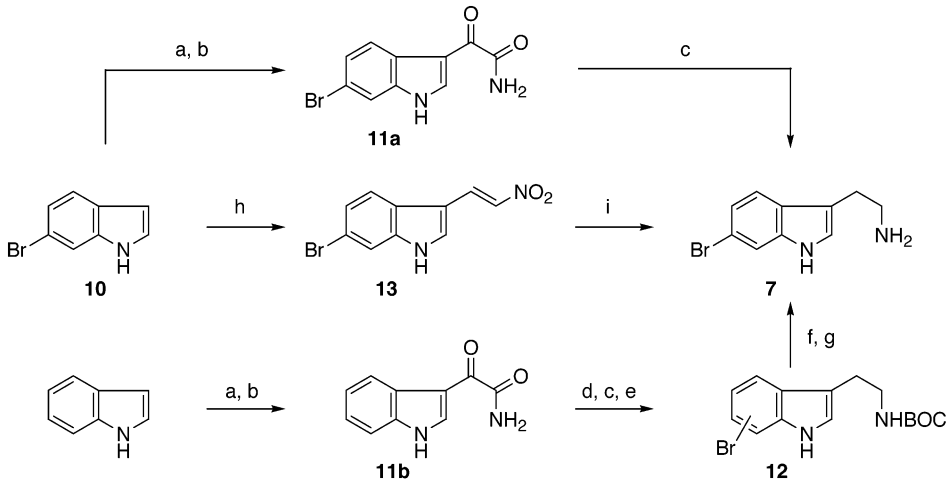


FIGURE 1. Retrosynthetic analysis for arborescidines A−C.

SCHEME 1[a]



[a] Reagents and conditions: (a) $(COCl)_2$, Et_2O, 0 °C, 2 h. (b) NH_4OH, 50 °C, 30 min, 77%. (c) $BH_3{\cdot}SMe_2$, THF, reflux, 2 h; then HCl (1 M), reflux, 3 h, 30%. (d) Br_2, AcOH, 15 °C, 40 min. (e) $(Boc)_2O$, CH_2Cl_2, 30 min. (f) chromatographic separation, 15%. (g) 25% aq HCl, EtOH, 30 min, quantitative. (h) $Me_2NCH{=}CHNO_2$, TFA, rt, 30 min, 96%. (i) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF, reflux, 2 h; then HCl (1 M), reflux, 2 h; NaOH, 73%.

synthesis of substituted indoles from benzenoid precursors. Among these, the Fischer,[7] Reissert,[8] and Batcho−Leimgruber[9] indole syntheses have been widely utilized for the synthesis of 4-, 5-, 6-, and 7-substituted indoles. For the present project, we required an efficient synthesis of 6-bromotryptamine (**7**), which was a key precursor to *β*-carbolines **6** and **8** (Scheme 1). We have examined several of the reported methods to **7**, and have found the Schumaker and Davidson[10] method to be the most efficient.

The precursor to tryptamine **7** is 6-bromoindole (**10**), which was prepared by a modified Batcho−Leimgruber indole synthesis as reported by Rapoport et al.[11] The reaction of **10** with $(COCl)_2$, followed by treatment with aqueous NH_4OH, afforded 3-glyoxyamide-6-bromoindole (**11a**), which upon borane reduction gave **7**, albeit in low yield (30%).

In another approach, glyoxyamide **11b** was prepared from indole through the same steps described above for **11a** and was submitted to the following reaction sequence: (1) bromination to afford a mixture of 5- and 6-bromo glyoxyamides, (2) borane reduction, and (3) *N*-Boc protection to give a mixture of 5- and 6-bromo-*N*-Boc bromotryptamines **12** in 30% overall yield, which after column chromatography separation and *N*-Boc deprotection afforded **7** in 15% overall yield (Scheme 1).[4] The most efficient route to **7** was through nitroethylene

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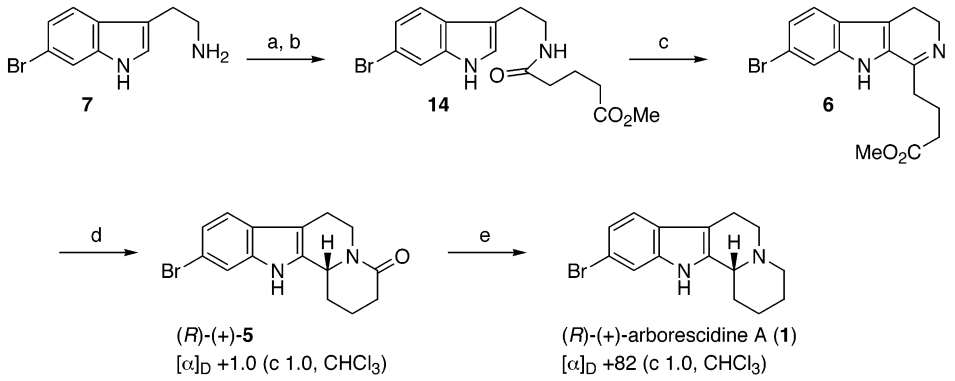
SCHEME 2[a]



[a] Reagents and conditions: (a) glutaric anhydride, CH_2Cl_2, 0 °C to rt, 10 min. (b) $SOCl_2$, MeOH, 0 °C to rt, 3 h, 83%. (c) $POCl_3$, benzene, reflux, 2 h, 86%. (d) (*S*,*S*)-TsDPEN−Ru(II) complex, HCO_2H−Et_3N (5:2), DMF, rt, 12 h, 89%. (e) AlH_3, THF, rt, 10 min, 78%.

13. The reaction of **10** with 1-(dimethylamino)-2-nitroethylene (DMANE)[12] in the presence of TFA afforded 3-[(*E*)-2-nitroethenyl]-6-bromoindole (**13**) in 96% yield. Attempted reduction of **13** to **7** with $LiAlH_4$ in THF gave a mixture in which the debrominated product predominated. On the other hand, reduction with borane, which was generated in situ as described by Schumaker and Davidson,[10] proceeded smoothly to provide **7** in 73% yield.

With an efficient route to **7** in hand, we directed our efforts to the synthesis of arborescidine A, following the sequence depicted in Scheme 2. Thus, exposure of **7** to glutaric anhydride in CH_2Cl_2 at room temperature formed the corresponding amide carboxylic acid, which upon treatment with $SOCl_2$/MeOH afforded methyl ester **14** in 83% yield (two steps). Treatment of amide **14** with $POCl_3$ promoted the Bischler−Napieralsky cyclization to produce imine **6** in 86% yield.

Having prepared β-carboline imine **6**, the stage was set to introduce the required asymmetry through the Noyori asymmetric hydrogen-transfer reaction.[5] In Nature, oxidoreductases catalyze remarkably selective transfer hydrogenations of carbonyl compounds to alcohols using cofactors such as NADH or NADPH.[13] Noyori and co-workers have shown that *p*-cymene−Ru(II) complexes of certain chiral 1,2-diamines are highly effective as catalysts for the asymmetric reduction of imines. This method uses a formic acid−triethylamine azeotropic mixture as the reductant and provides a convenient, general route to natural and unnatural β-carboline alkaloids.

The Noyori reduction of imine **6** was accomplished with preformed (*S*,*S*)-TsDPEN−Ru(II) complex in DMF and a HCO_2H−Et_3N mixture, which afforded, after in situ cyclization, lactam **5** in 89% yield and 96% ee, as determined by HPLC analysis using a ChiralCel OD column. On the basis of the examples that have been reported by Noyori, the absolute stereochemistry of **5** is expected to be *R*, as shown. This outcome is consistent with the general model that Noyori had proposed, depicted in Figure 2, for the asymmetric hydrogen-transfer reactions with TsDPEN−Ru(II) complexes. The chiral ruthenium species in the stereodeterminant hydrogen-transfer step discriminates between the enantiofaces of the cyclic imine. The hydride transfer from the ruthenium species to an imine requires an out-of-plane interaction between the Ru−H moiety and the C=N bond. It is likely that the hydrogen transfer occurs via a metal−ligand bifunctional catalysis[14] and the NH linkage further stabilizes the transition state by forming a hydrogen bond with the nitrogen of the imine, as shown in **I**, Figure 2.[14b] Thus, on the basis of this model, the use of (*S*,*S*)-TsDPEN−Ru(II) complex in the hydrogen transfer is expected to occur from the *si* face of imine **6** to provide (*R*)-**5**.

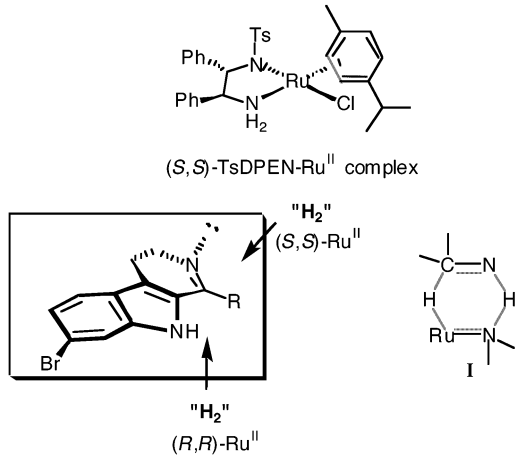


FIGURE 2. Asymmetric hydrogen-transfer reaction of beta-carbolines catalyzed by Ru(II) complex.[14]

Exposure of lactam **5** to borane reduction in THF resulted in the formation of the desired product (+)-arborescidine A ((+)-**1**), albeit in disappointingly low yield (10%). On the other hand, reduction of lactam **5** proceeded smoothly with AlH_3[15] at room temperature to furnish (+)-**1** in 78% yield. The optical rotation of our synthetic arborescidine A, $[\alpha]_D$ +82 (c = 1, $CHCl_3$), was opposite that reported for natural arborescidine A, $[\alpha]_D$ −82 (c = 1, $CHCl_3$).[2] Our result supports the *S* absolute stereochemistry originally assigned to arborescidine A.

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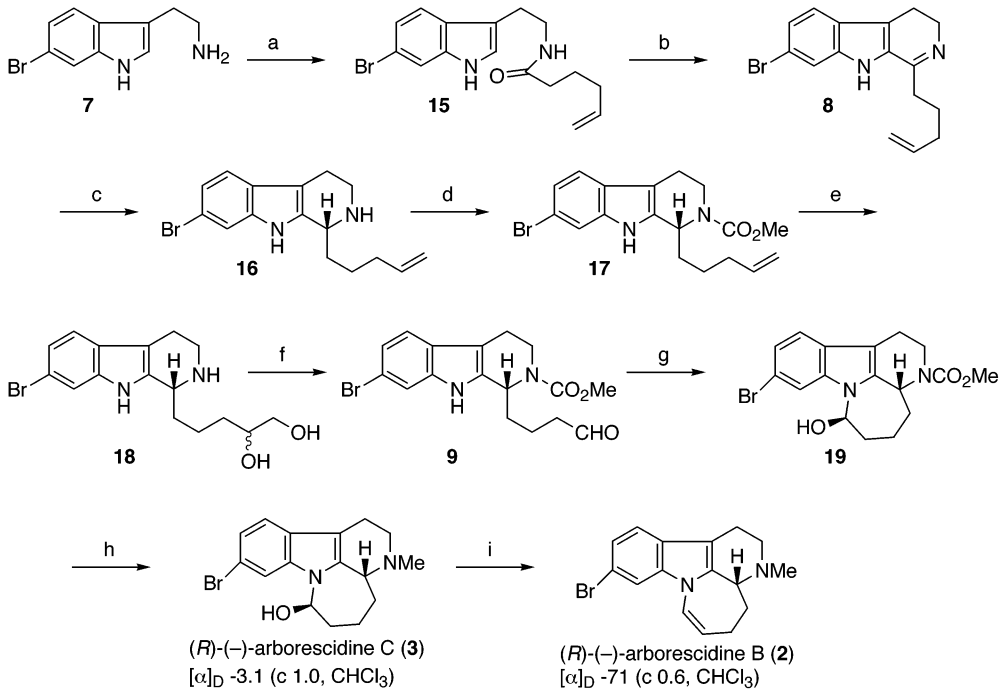
SCHEME 3[a]



[a] Reagents and conditions: (a) 5-hexenoic acid, HOBt, EDC, CH_2Cl_2, rt, 10 h, 99%. (b) $POCl_3$, MeCN, reflux, 3 h, 90%, or $POCl_3$, benzene, reflux, 2.5 h, 75%. (c) (*S*,*S*)-TsDPEN−Ru(II) complex, HCO_2H−Et_3N (5:2), DMF, rt, 12 h, 96%. (d) MeOCOCl, Et_3N, CH_2Cl_2, 99%. (e) OsO_4/*t*-BuOH, NMO, THF−H_2O, 0 °C to rt, 10 h, 88%. (f) $NaIO_4$, THF−H_2O (1:2), 90%. (g) aq TFA, THF, 1 h, 95% (>20:1 *trans*/*cis*). (h) AlH_3, THF, rt, 15 min, 96%. (i) $MeO_2CNSO_2NEt_3$, benzene, 8 h, 84%.

With an efficient approach to arborescidine A secured, the stage was now set for the total synthesis of arborescidines B and C. Treatment of **7** with 5-hexenoic acid[16] in the presence of EDC/HOBt gave amide **15** in 99% yield (Scheme 3). This compound was also prepared through the reaction of the corresponding acyl chloride ($SOCl_2$, 0 °C to rt, 98%) with **7** in the presence of K_2CO_3 in CH_2Cl_2 (95% yield) or MeCN (90% yield).

The Bischler−Napieralsky reaction in benzene afforded imine **8** in 75% yield from **15**, and this yield was improved to 90% when the reaction was carried out in acetonitrile. Noyori asymmetric hydrogen-transfer reaction of imine **8** in DMF afforded amine **16** in 96% yield. Interestingly, when the imine was subjected to Noyori asymmetric hydrogen-transfer reaction in acetonitrile as the solvent, in accordance with a described procedure,[17] no reaction took place, only the starting material being observed. At this stage, the free amine **16** was converted to the corresponding methyl carbamate **17**, and the enantiomeric excess was determined by HPLC analysis (93% ee).

With asymmetry incorporated, we turned our attention to the exploration of methods for the oxidative cleavage of the alkene moiety. The carbamate group of **17** was required for dihydroxylation of the double bond. Attempts to use the corresponding *N*-methyl derivative of **16** in the dihydroxylation step failed, despite attempts under several different conditions, such as AD-mix, NMO/OsO_4, and catalytic K_2OsO_4/$NaIO_4$/EtOAc−H_2O. The dihydroxylation of carbamate **17** (OsO_4/*t*-BuOH, NMO in THF−H_2O at 0 °C to room temperature, 88% yield), on the other hand, proceeded well provided the reaction was carried out in the dark. Surprisingly, it was noted that if the reaction flask was not protected from light the yields decreased significantly.

Oxidative cleavage of diol **18**, accomplished using $NaIO_4$ in a THF−H_2O (1:2 v/v) mixture, proceeded cleanly to give the rather unstable aldehyde **9** in excellent yield (90%). Treatment of the crude aldehyde **9** with aqueous TFA in THF afforded a >20:1 mixture of *trans*/*cis*-**19** (95% yield), which after AlH_3 reduction provided **3** in 96% yield (mp 171−172 °C, lit.[2] mp 172−173 °C). As with arborescidine A, the sign of the absolute configuration of our synthetic sample, $[\alpha]_D$ −3.1 (c = 1, $CHCl_3$), was opposite that reported for natural arborescidine C, lit.[2] $[\alpha]_D$ +3 (c = 1, $CHCl_3$).

Finally, the conversion of **3** to arborescidine B requires only dehydration of the alcohol. This was best accomplished using the Burgess reagent in benzene,[18] which afforded **2** in 84% yield. As was observed for the other arborescidines, synthetic **2** displayed the opposite absolute configuration, $[\alpha]_D$ −71 (c = 0.6, $CHCl_3$), when compared to natural **2**, $[\alpha]_D$ +70 (c = 0.6, $CHCl_3$).[2]

In conclusion, we have completed the first enantioselective total syntheses of (+)-arborescidine A ((+)-**1**), (−)-arborescidine B ((−)-**2**), and (−)-arborescidine C

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((−)-**3**), via routes that proceeded in five steps and 50% overall yield, eight steps and 61% overall yield, and nine steps and 51% overall yield, respectively, from **7**. The syntheses feature the use of the Noyori catalytic asymmetric hydrogen-transfer reaction to introduce the chirality in dihydro-*β*-carbolines **6** and **8**. The reductions were performed using the (*S*,*S*)-TsDPEN−Ru(II) catalyst, which, on the basis of the ample precedent from Noyori's work, produced chiral dihydro-*β*-carbolines—and ultimately the natural products—possessing the *R* absolute configuration. The optical rotations of our synthetic arborescidines were opposite in sign those of the natural products. Taken together, our results support the *S* configuration for natural **1** and **2** as well as the (3*S*,17*S*) configuration for natural **3**.

Experimental Section

Methyl 4-[2-(6-Bromo-1*H*-3-indolyl)ethylcarbamoyl]-butanoate (14). Glutaric anhydride (63.5 mg, 0.556 mmol) was added to a solution of 6-bromotryptamine (**7**)[10] (0.133 g, 0.556 mmol) in CH_2Cl_2 (5.6 mL) at 0 °C. The mixture was warmed to room temperature, concentrated in vacuo, and used without purification in the esterification step. To a solution of crude acid in dry MeOH (1.0 mL) was added $SOCl_2$ (40.4 μL, 0.556 mmol) at 0 °C. The mixture was stirred for 3 h, then neutralized with saturated aq $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography ($CHCl_3$/MeOH, 10%, R_f = 0.79) afforded a white solid, which was characterized as **14** in 83% yield. Mp: 159.7−160.1 °C. ^{1}H NMR (d_6-DMSO, 300 MHz): δ 1.73 (2H, quint, J = 7.3 Hz), 2.08 (2H, t, J = 7.3 Hz) 2.26 (2H, t, J = 7.3 Hz), 2.78 (2H, t, J = 7.3 Hz), 3.30 (2H, q, J = 7.3 Hz), 3.57 (3H, s), 7.09 (1H, dd, J = 8.4 and 0.7 Hz), 7.16 (1H, br s), 7.47 (1H, d, J = 1.5 Hz), 7.50 (1H, d, J = 1.5 Hz), 7.89 (1H, t, J = 5.5 Hz), 10.94 (1H, s). ^{13}C NMR (d_6-DMSO, 75 MHz): δ 20.5, 25.0, 32.7, 34.4, 40.1, 51.2, 112.2, 113.6, 113.8, 119.9, 120.9, 123.6, 126.2, 136.9, 171.1, 172.8. IR (KBr film, cm^{-1}): 3317, 3186, 3101, 3059, 2951, 2906, 2879, 2854, 1711, 1631, 1545, 1442, 1315, 1201, 791, 678. HRMS (70 eV): $C_{16}H_{19}N_2O_3Br$ *m*/*z* calcd 366.0579, found 366.0577.

Methyl 4-(7-Bromo-4,9-dihydro-3*H*-*β*-carbolin-1-yl)butanoate (6). Amido ester **14** (0.136 g, 0.371 mmol) in 9.25 mL of dry benzene and 242 μL of $POCl_3$ was heated to reflux for 2 h, cooled to room temperature, and then concentrated. The resulting orange viscous oil was purified by chromatography (CH_3Cl/MeOH, 10%, R_f = 0.30) to afford a yellow solid in 86% yield, which was characterized as imine **6**. Mp: 151.3−152.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.94−2.06 (2H, m), 2.50 (2H, t, J = 6.2 Hz), 2.65 (2H, t, J = 7.7 Hz), 2.84 (2H, t, J = 9.1 Hz), 3.77 (3H, s), 3.87 (2H, t, J = 8.4 Hz) 7.21 (1H, dd, J = 8.4 and 1.5 Hz), 7.42 (1H, d, J = 8.4 Hz), 7.60 (1H, d, J = 1.5 Hz), 10.14 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.2, 22.0, 32.7, 35.1, 48.2, 52.1, 115.0, 116.2, 117.5, 120.9, 123.2, 124.2, 128.8, 137.3, 160.3, 175.1. IR (KBr film, cm^{-1}): 3348, 3016, 2924, 2846, 1736, 1620, 1543, 1435, 1365, 1311, 1242, 1041, 802, 756. HRMS (70 eV): $C_{16}H_{17}N_2O_2Br$ *m*/*z* calcd 348.0473, found 348.0474.

(12b*R*)-10-Bromo-1,2,3,4,6,7,12,12b-octahydropyrido-[2,1-*a*]-*β*-carbolin-4-one (5). A solution of *p*-TsCl (0.45 g, 2.40 mmol) in 5 mL of dry THF was added to a mixture of (1*S*,2*S*)-(+)-1,2-diphenylethylenediamine (0.50 g, 2.40 mmol) in THF (20 mL) and triethylamine (1.0 mL) over a period of 30 min at 0 °C. After the resulting solution was stirred for 12 h, the solvent was removed under reduced pressure. The solid residue was treated with aqueous saturated $NaHCO_3$ solution (40 mL) and CH_2Cl_2 (40 mL). The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The crude product was purified by column chromatography with ethyl acetate to afford (1*S*,2*S*)-1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine (0.79 g, 2.16 mmol, 92%) as a cream-colored solid that was identical spectroscopically to the previously reported compound.[17] The (*S*,*S*)-TsDPEN−Ru(II) complex was prepared by stirring 4.56 μg (7.44 μmol) of dichloro(η^6-*p*-cymene)-ruthenium(II) dimer, 2.72 μg of (1*S*,2*S*)-1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine, and triethylamine (1.04 μL) in degassed dry DMF (0.5 mL) at 90 °C for 1 h. Then, the preformed catalyst solution was added to a mixture of imine **6** (0.130 g, 0.372 mmol) in 3.7 mL of DMF, followed by a mixture of HCO_2H-Et_3N (5:2 v/v, 19.0 μL) at room temperature. After the resulting solution was stirred at room temperature for 12 h, the DMF was distilled off under high vacuum, and the crude purified by flash chromatography ($CHCl_3$/MeOH, 10%, R_f = 0.7) to afford 0.106 g (89%) of lactam **5** as a creamy solid. $[\alpha]_D$ +1.0 (c = 1, $CHCl_3$). Mp: 242−243 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.71−1.94 (3H, m), 2.34−2.66 (2H, m), 2.73 (1H, m), 2.84 (2H, d, J = 9.5 Hz), 2.94 (1H, d, J = 22.7 Hz), 4.74 (1H, br dd, J = 9.1 and 3.3 Hz), 5.16 (1H, d, J = 8.8 Hz), 7.19 (1H, dd, J = 8.4 and 0.7 Hz), 7.33 (1H, d, J = 8.4 Hz), 7.46 (1H, s), 8.62 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.4, 21.0, 29.0, 32.5, 40.1, 54.4, 109.4, 113.9, 115.2, 119.5, 122.9, 125.7, 134.0, 137.0, 169.1. IR (KBr film, cm^{-1}): 3265, 3101, 2924, 2854, 1616, 1462, 1442, 1311, 1269, 1232, 1038, 754. HRMS (70 eV): $C_{15}H_{15}N_2OBr$ *m*/*z* calcd 318.0368, found 318.0366.

(+)-Arborescidine A ((+)-1). To a solution of lactam **5** (0.160 g, 0.502 mmol) in dry THF (6.0 mL) was added a solution of AlH_3 in THF (1.55 M, 1.94 mL, 3.01 mmol)[15] at room temperature. After 10 min, the reaction was quenched with saturated aq sodium sulfate solution and filtered. The solids were washed with CH_2Cl_2 (200 mL), dried with Na_2SO_4, and evaporated in vacuo. Purification by chromatography eluting with EtOAc/Et_3N (5%) afforded a white solid in 78% yield, which was characterized as arborescidine A (**1**), in full agreement with the reported data.[2] $[\alpha]_D$ +82 (c = 1, $CHCl_3$). Mp: 203−204 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.44−1.48 (1H, m), 1.49−1.65 (1H, m), 1.70−1.79 (2H, m), 1.86−1.97 (1H, m), 2.03−2.09 (1H, m), 2.34−2.42 (1H, m), 2.57−2.69 (2H, m), 2.92−3.09 (3H, m), 3.19 (1H, d, J = 8.8 Hz), 7.16 (1H, dd, J = 8.4 and 1.5 Hz), 7.30 (1H, d, J = 8.4 Hz), 7.42 (1H, d, J = 1.5 Hz), 7.75 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 24.3, 25.7, 29.9, 53.4, 55.7, 60.0, 108.3, 113.7, 114.5, 119.3, 122.7, 126.4, 135.8, 136.7. HRMS (70 eV): $C_{15}H_{17}N_2OBr$ *m*/*z* calcd 304.0575, found 304.0574.

***N*1-[2-(6-bromo-1*H*-3-indolyl)ethyl]-5-hexenamide (15).** To a solution of **7** (0.284 g, 1.19 mmol) and 5-hexenoic acid (0.136 g, 1.19 mmol) in CH_2Cl_2 (12.0 mL) at 0 °C were added HOBt (0.177 g, 1.31 mmol) and EDC (0.251 g, 1.31 mmol). The reaction mixture was stirred at room temperature for 10 h, then washed with 5% aqueous HCl (3 × 15.0 mL), 5% aqueous $NaHCO_3$ (20.0 mL), H_2O (20.0 mL), and brine (20.0 mL), and dried (Na_2SO_4). Purification by flash chromatography (CH_3Cl/MeOH, 10%, R_f = 0.43) afforded amidoalkene **15** in 99% yield as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.70 (2H, quint, J = 7.6 Hz), 2.03 (2H, q, J = 7.1 Hz), 2.14 (2H, t, J = 7.7 Hz), 2.93 (2H, t, J = 6.8 Hz), 3.56 (2H, q, J = 6.5 Hz), 4.96 (1H, d, J = 10.3 Hz), 4.97 (1H, d, J = 17.6 Hz), 5.64 (1H, br s), 5.73 (1H, ddt, J = 17.6, 10.3, and 6.5 Hz), 6.97 (1H, d, J = 1.3 Hz), 7.19 (1H, dd, J = 8.4 and 0.9 Hz), 7.43 (1H, d, J = 8.4 Hz), 7.51 (1H, s), 8.67 (1H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.6, 25.2, 33.0, 35.9, 39.7, 112.9, 114.2, 115.3, 115.6, 119.8, 122.6, 122.6, 126.2, 137.1, 137.8, 173.0. IR (KBr film, cm^{-1}): 3288, 3076, 2931, 2861, 1647, 1542, 1456, 1417, 912, 802. HRMS (70 eV): $C_{16}H_{19}N_2OBr$ *m*/*z* calcd 334.0681, found 334.0683.

7-Bromo-1-(4-pentenyl)-4,9-dihydro-3*H*-*β*-carboline (8). A solution of **15** (1.65 g, 4.94 mmol) and 3.21 mL of $POCl_3$ in 123 mL of dry MeCN was heated to reflux for 3 h, cooled to room temperature, and then concentrated. The resulting orange viscous oil was purified by flash chromatography (CH_3Cl/MeOH, 10%, R_f = 0.71) to afford a yellow oil in 90% yield. The spectroscopic properties of the product were in accordance

with imine **8**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.82 (2H, quint, J = 7.7 Hz), 2.11 (2H, q, J = 7.1 Hz), 2.70 (2H, t, J = 7.7 Hz), 2.87 (2H, t, J = 8.5 Hz), 3.89 (2H, t, J = 8.5 Hz), 4.91 (1H, dd, J = 10.3 and 1.5 Hz), 4.94 (1H, dd, J = 17.9 and 1.5 Hz), 5.73 (1H, ddt, J = 17.6, 10.3, and 6.7 Hz), 7.12 (1H, dd, J = 8.5 and 1.5 Hz), 7.45 (1H, d, J = 8.5 Hz), 7.52 (1H, d, J = 1.5 Hz), 9.99 (1H, br s). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.2, 26.0, 33.3, 34.7, 47.7, 114.8, 114.9, 115.3, 116.9, 117.7, 121.2, 123.5, 124.3, 129.2, 137.6, 161.6. HRMS (70 eV): $C_{16}H_{17}N_2Br$ m/z calcd 316.0575, found 316.0554.

(*R*)-7-Bromo-1-(4-pentenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline (16). The preformed catalyst solution (prepared as described previously) was added to a mixture of imine **8** (0.750 g, 2.37 mmol) in 24 mL of DMF, followed by a mixture of HCO_2H-Et_3N (5:2 v/v, 1.22 mL) at room temperature. After the resulting solution was stirred at room temperature for 12 h, the DMF was distilled off under a high vacuum, and the crude purified by flash chromatography ($CHCl_3$/MeOH, 10%, R_f = 0.52) to afford 0.726 g (96%) of amine **16** as a brown solid. $[\alpha]_D$ −21 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.51−1.69 (4H, m), 1.70−74 (1H, m), 2.11 (2H, quint, J = 6.5 Hz), 2.64−2.74 (2H, m), 3.00 (1H, ddd, J = 12.8, 8.5, and 5.5 Hz), 3.33 (1H, dt, J = 13.0 and 4.5 Hz), 4.01 (1H, ddd, J = 8.5, 3.5, and 2.0 Hz), 4.98 (1H, br dd, J = 10.0 and 1.5 Hz), 5.03 (1H, dd, J = 17 and 1.5 Hz), 5.80 (1H, ddt, J = 17.0, 13.0, and 10.0 Hz), 7.16 (1H, dd, J = 8.5 and 1.5 Hz), 7.31 (1H, d, J = 8.5 Hz), 7.38 (1H, d, J = 1.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.5, 24.9, 33.6, 34.1, 42.3, 52.4, 109.0, 113.6, 114.5, 115.0, 119.12, 122.4, 126.4, 136.4, 136.9, 138.3. HRMS (70 eV): $C_{16}H_{19}N_2Br$ m/z calcd 318.0732, found 318.0730.

(*R*)-Methyl 7-Bromo-1-(4-pentenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-2-carboxylate (17). To a cold solution of amine **16** (1.81 g, 5.67 mmol) and triethylamine (0.861 g, 8.50 mmol) in dry CH_2Cl_2 (94.0 mL) kept at 0 °C was added dropwise a solution of methyl chloroformate (1.07 g, 11.3 mmol) in CH_2Cl_2 (10 mL). After 1 h, the reaction mixture was diluted with water (60.0 mL), followed by saturated aq NH_4Cl solution (100 mL) and extracted with CH_2Cl_2. The organic layers were washed with saturated aq $NaHCO_3$ solution (100 mL) and water (100 mL) and dried. The solvent was removed and the residue purified by flash chromatography ($CHCl_3$/MeOH, 2.5%, R_f = 0.51) to give 2.12 g (99%) of **17** as a brown solid. $[\alpha]_D$ −3.9 (c = 1, $CHCl_3$). Mp: 62−63 °C. ^{1}H NMR (d_6-DMSO, 343 K, 400 MHz): δ 1.45−1.55 (2H, m), 1.73−1.82 (1H, m), 1.89−1.91 (1H, m), 2.09 (2H, quint, J = 5.9 Hz), 2.64 (1H, dd, J = 5.9 and 2.2 Hz), 2.63−2.67 (1H, m), 3.16 (1H, ddd, J = 12.8, 10.2, and 6.6 Hz), 3.66 (3H, s), 4.25 (1H, dd, J = 15.2 and 3.2 Hz), 4.96 (1H, dd, J = 10.3 and 1.5 Hz), 5.02 (1H, dd, J = 17.1 and 1.5 Hz), 5.16 (1H, dd, J = 9.2 and 4.1 Hz), 5.82 (1H, ddt, J = 17.1, 10.3, and 6.7 Hz), 7.07 (1H, dd, J = 8.4 and 1.5 Hz), 7.31 (1H, d, J = 8.4 Hz), 7.48 (1H, d, J = 1.5 Hz), 10.83 (1H, s). ^{13}C NMR (d_6-DMSO, 343 K, 100 MHz): δ 20.3, 24.6, 32.5, 33.4, 37.5, 50.7, 51.9, 106.6, 113.1, 113.3, 114.3, 118.8, 121.0, 125.2, 135.6, 136.6, 138.1, 155.4. IR (KBr film, cm^{-1}): 3306, 1680. HRMS (70 eV): $C_{18}H_{21}N_2O_2Br$ m/z calcd 376.0786, found 376.0788.

Methyl (1*R*,4′*R*)- and (1*R*,4′*S*)-7-Bromo-1-(4′,5′-dihydroxypentyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-2-carboxylates (18). Osmium tetroxide (67.0 μL of a freshly prepared 0.039 M solution in *t*-BuOH) was added to a solution of **17** (0.283 g, 0.775 mmol) and *N*-methylmorpholine *N*-oxide (0.256 mL, 50% v/v in water) in a 9:1 THF−H_2O solution (9.70 mL) at 0 °C. After 12 h at room temperature, the mixture was treated with Florisil (0.350 g) and $NaHSO_3$ (0.111 g), stirred for 1 h, filtered, and concentrated. The residue was diluted with EtOAc, and the organic layer was washed with 5% H_3PO_4 and brine, dried, and concentrated. Purification by flash chromatography (CH_3Cl/MeOH, 10%, R_f = 0.45) gave a mixture of diols **18** (0.280 g, 88%). ^{1}H NMR (d_6-DMSO, 343 K, 400 MHz): δ 1.37−1.55 (4H, m), 1.77−1.98 (2H, m), 2.65 (2H, dd, J = 8.9 and 3.3 Hz), 3.17 (1H, dt, J = 13.0 and 7.9 Hz), 3.29 (2H, dd, J = 5.5, and 1.1 Hz), 3.41−3.48 (1H, m), 3.65 (3H, s), 4.26 (1H, br d, J = 13.0 Hz), 5.15 (1H, dd, J = 8.9 and 4.2 Hz), 7.07 (1H, dd, J = 8.4 and 1.5 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.47 (1H, d, J = 1.5 Hz), 10.83 (1H, s). ^{13}C NMR (d_6-DMSO, 343 K, 100 MHz): δ 20.3, 21.4, 32.9, 33.9, 37.5, 50.9, 51.9, 65.6, 70.7, 106.5, 113.0, 113.3, 118.8, 120.9, 125.2, 135.8, 136.5, 155.4. IR (KBr film, cm^{-1}): 3400, 1679. HRMS (70 eV): $C_{18}H_{23}N_2O_4Br$ m/z calcd 410.0841, found 410.0845.

Methyl (1*R*)-7-Bromo-1-(3-formylpropyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-2-carbox ylate (9). A solution of **18** (0.240 g, 0.584 mmol) in 58.4 mL of THF−H_2O (1:2) was treated at 0 °C with a solution of 0.131 g (0.613 mmol) of sodium metaperiodate ($NaIO_4$) in 6 mL of water. After the resulting solution was stirred for 1 h at 0 °C, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with brine, dried, and concentrated in vacuo to give aldehyde **9** as a cream-colored solid in 90% yield. Mp: 64−65 °C. R_f = 0.83 ($CHCl_3$/MeOH, 10%). $[\alpha]_D$ −47 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.77−1.92 (4H, m), 2.47−2.52 (2H, m), 2.65 (1H, dd, J = 15.4 and 3.6 Hz), 2.72−2.84 (1H, m), 3.11−3.22 (1H, m), 3.77 (3H, s), 4.32−4.49 (1H, m), 5.16−5.30 (1H, m), 7.17 (1H, dd, J = 8.5 and 1.3 Hz), 7.29 (1H, d, J = 8.3 Hz), 7.42 (1H, d, J = 1.3 Hz), 8.43 and 8.75 (1H, br s and br s), 9.69 and 9.76 (1H, br s and br s). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.4, 21.0, 33.9, 38.4, 43.3, 51.0, 52.6, 108.2, 113.9, 115.0, 119.2, 122.6, 125.6, 134.7, 136.9, 156.5, 202.4. IR (KBr film, cm^{-1}): 3309, 1699, 1681. HRMS (70 eV): $C_{17}H_{19}N_2O_3Br$ m/z calcd 378.0579, found 378.0578.

Methyl (3a*R*,7*R*)-10-Bromo-7-hydroxy-1,2,3,3a,4,5,6,7-octahydroazepino[1,2,3-*lm*]-β-carboline-3-carboxylate (19). To a solution of aldehyde **9** (0.185 g, 0.488 mmol) in 0.80 mL of THF was added aqueous TFA (3.75 mL, 10% v/v in water). The reaction mixture was stirred for 1 h at room temperature, treated with saturated aq Na_2CO_3 (pH 9), and stirred for another 1 h. The product was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with H_2O and brine and dried over Na_2SO_4. The solvent was removed and the residue purified by flash chromatography ($CHCl_3$/MeOH, 10%, R_f = 0.76) to give 0.176 g (95%) of **19** as a colorless oil. $[\alpha]_D$ −25 (c = 1, $CHCl_3$). ^{1}H NMR (d_6-DMSO, 343 K, 400 MHz): δ 1.69−1.82 (3H, m), 1.92−1.98 (1H, m), 2.20−2.25 (2H, m), 2.62−2.70 (2H, m), 3.06 (1H, ddd, J = 12.8, 11.2, and 4.79 Hz), 3.69 (3H, s), 4.30 (1H, dd, J = 12.6 and 3.0 Hz), 5.30 (1H, d, 10.9), 6.17 (1H, d, J = 4.2 Hz), 6.29 (1H, br s, OH), 7.12 (1H, dd, J = 8.4 and 1.4 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.70 (1H, br s). ^{13}C NMR (d_6-DMSO, 343 K, 100 MHz): δ 18.9, 20.7, 32.8, 33.8, 38.1, 51.8, 75.1, 78.7, 107.6, 112.1, 113.5, 118.9, 121.2, 124.4, 136.2, 136.4, 154.6. IR (KBr film, cm^{-1}): 3380, 1678. HRMS (70 eV): $C_{17}H_{19}N_2O_3Br$ m/z calcd 378.0579, found 378.0782.

(−)-Arborescidine C ((−)-3). To a solution of **19** (0.097 g, 0.256 mmol) in dry THF (4.3 mL) was added a solution of AlH_3 in THF (1.55 M, 0.330 mL, 0.512 mmol)[15] at room temperature. After 10 min, the reaction was quenched with saturated aq sodium sulfate solution and filtered. The solids were washed with CH_2Cl_2 (50 mL), and the filtrate was dried with Na_2SO_4, evaporated, and concentrated in vacuo. Purification of the residue by column chromatography (elution with 10% $CHCl_3$/MeOH, R_f = 0.4) afforded a white solid in 96% yield, which was characterized as arborescidine C, in full accordance with the reported data.[2] Mp: 171−172 °C. $[\alpha]_D$ −3.1 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.33 (1H, q dist, J = 15.6 Hz), 1.52 (1H, t, J = 16.6 Hz), 1.73 (1H, br d, J = 16.6 Hz), 2.07 (1H, q, J = 15.8 Hz), 2.13 (1H, d, J = 14.5 Hz), 2.23 (1H, br d, J = 16.7 Hz), 2.37 (3H, s), 2.60−2.70 (3H, m), 2.89 (1H, dd, J = 13.3 and 5.9 Hz), 3.55 (1H, d, J = 13.9 Hz), 6.00 (1H, d, J = 2.9 Hz), 7.14 (1H, d, J = 10.2 Hz), 7.22 (1H, d, J = 10.2 Hz), 7.41 (1H, s). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.3, 20.5, 31.5, 34.5, 42.8, 50.2, 61.1, 76.8, 108.9, 111.9, 114.9, 119.7, 122.6, 125.8, 137.1, 138.5. HRMS (70 eV): $C_{16}H_{19}N_2OBr$ m/z calcd 334.0681, found: 334.0733.

(−)-Arborescidine B ((−)-2). A solution of arborescidine C (0.030 g, 0.0896 mmol) and Burgess reagent (0.043 g, 0.179

mmol) in dry benzene (9.0 mL) was heated to reflux for 8 h under nitrogen atmosphere. The reaction solution was cooled, diluted with EtOAc (9.0 mL), washed with brine (4 × 9.0 mL), dried, and evaporated. Column chromatography of the residue over silica gel (10% $CHCl_3$/MeOH, $R_f = 0.64$) gave arborescidine B (**2**) as a colorless oil in 84% yield. $[\alpha]_D$ −71 ($c = 0.6$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.86 (1H, dq, $J = 10.0$ and 4.3 Hz), 2.35−2.36 (1H, m), 2.40−2.44 (1H, m), 2.49−2.57 (1H, m), 2.54 (3H, s), 2.68 (1H, dd, $J = 12.4$ and 4.1 Hz), 2.70 (1H, dd, $J = 11.2$ and 3.9 Hz), 2.89 (1H, dddd, $J = 15.0$, 11.2, 2.6, and 2.4 Hz), 3.12 (1H, ddd, $J = 15.0$, 11.2, and 2.4 Hz), 3.36 (1H, d, $J = 10.0$ Hz), 5.09 (1H, dt, $J = 9.8$ and 4.1 Hz), 6.81 (1H, dt, $J = 9.8$ and 1.8 Hz), 7.21 (1H, dd, $J = 9.8$ and 1.5 Hz), 7.31 (1H, br d, $J = 9.8$ Hz), 7.47 (1H, d, $J = 1.5$ Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.6, 27.9, 29.8, 42.4, 52.6, 62.3, 76.8, 109.3, 111.2, 112.3, 115.2, 119.3, 121.6, 123.2, 125.8, 136.9. IR (KBr film, cm^{-1}): 1674. HRMS (70 eV): $C_{16}H_{17}N_2Br$ *m*/*z* calcd 316.0575, found 316.0539.

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Supporting Information Available: Copies of the ^{1}H and ^{3}C NMR spectra of compounds **1**, **2**, **3**, **5**, **6**, **8**, **17**, and **19** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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