Studies of Palladium-Catalyzed Cross-Coupling Reactions for Preparation of Highly Hindered Biaryls Relevant to the Korupensamine/Michellamine Problem

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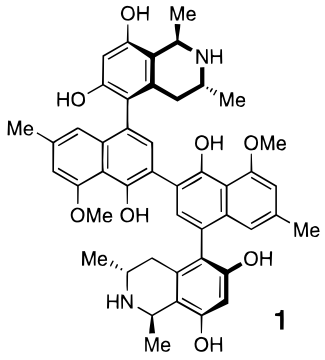
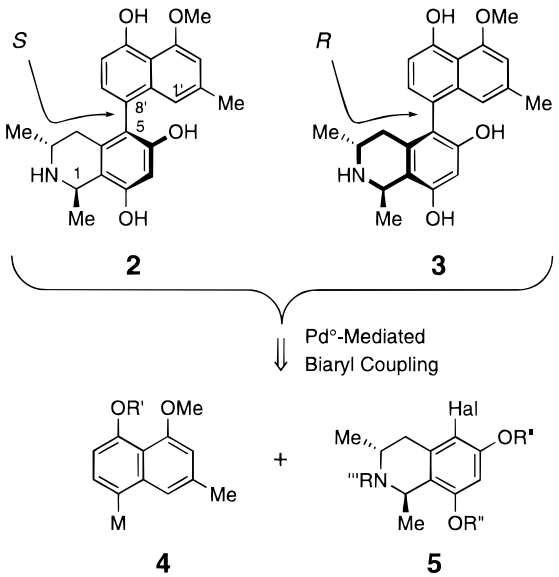
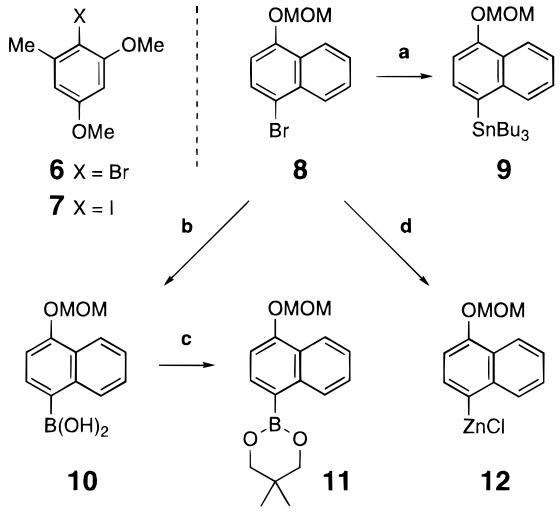
Recently, the isolation, structure assignment, and anti-HIV activity of three naturally occurring, atropisomeric alkaloids, michellamines A, B (**1**), and C, were described.[1] The michellamines have been prepared by total synthesis,[2] and two of the routes[2a,c] have passed through the monomers, korupensamine A (**2**) and B (**3**), which coexist in the liana, *Ancistrocladus korupensis*.[3,4] All have used palladium coupling steps to construct the key naphthalene−tetrahydroisoquinoline biaryl bond (cf., **4** + **5** to protected **2** and **3**). We describe here a comparative study of different versions (organostannanes or Stille,[5] organoboranes or Suzuki,[6] and organozincs or Negishi[7]) of the Pd^0-catalyzed construction of hindered biaryl bonds such as that found in **1**−**3**.





As model compounds, 2-bromo- and 2-iodo-3,5-dimethoxytoluene (**6** and **7**) were used because both the steric hindrance and electron density at the coupling positions are very similar to those of **5**, the ideal THIQ building block (Scheme 1). As model compounds for the naphthalene building block **4**, aryltin-, -boron-, and -zinc-containing reagents **9**−**12** were all prepared from bromide **8**, the MOM ether of 4-bromo-1-naphthol.

Scheme 1[a]



[a] (a) *n*-BuLi; *n*-Bu_3SnCl; (b) *n*-BuLi; $B(OMe)_3$; NH_4Cl; (c) 2,2-dimethylpropane-1,3-diol/PhMe/reflux; (d) *n*-BuLi; $ZnCl_2$/THF.

We first studied the Stille coupling reactions for this system. Stannane **9** was prepared in 79% yield after MPLC purification by metal−halogen exchange of **8** with *n*-BuLi and reaction with tributyltin chloride. Palladium-catalyzed Stille coupling reactions were then attempted (entries 1 and 2 in Table 1). A mixture of bromide **6** or iodide **7** and 2 equiv of stannane **9** and 10 mol % of $Pd(PPh_3)_4$ in toluene (0.1 M) was heated at 110 °C for 20 h in a sealed culture tube under N_2 (method A). Both reactions failed to provide any coupled product **13** under these conditions by GC/MS analysis, and considerable amounts of both starting materials remained. The *ortho*-disubstituted halides and the *ortho*-monosubstituted stannane are presumably too hindered to enter into the coupling event. When we tried the coupling reaction of 2-(tributylstannyl)furan (**14**) with iodide **7** under identical conditions, the coupled product **15** was isolated in excellent yield (90%). However, reaction of bromide **6** with stannane **14** again gave only starting materials. This demonstrated that the aryl iodide **7** is more reactive than bromide **6** and that the

(1) (a) Manfredi, K. P.; Blunt, J. W.; Cardellina, J. H., II; McMahon, J. B.; Pannell, L. L.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1991**, *34*, 3402. (b) Boyd, M. R.; Hallock, Y. F.; Cardellina, J. H., II; Manfredi, K. P.; Blunt, J. W.; McMahon, J. B.; Buckheit, R. W., Jr.; Bringmann, G.; Schaeffer, M.; Cragg, G. M.; Thomas, D. W.; Jato, J. G. *J. Med. Chem.* **1994**, *37*, 1740. (c) Bringmann, G.; Zagst, R.; Schaeffer, M.; Hallock, Y. F.; Cardellina, J. H., II; Boyd, M. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1190.

(2) (a) Bringmann, G.; Harmsen, S.; Holenz, J.; Geuder, T.; Goetz, R.; Keller, P. A.; Walter, R.; Hallock, Y. F.; Cardellina, J. H., II; Boyd, M. R. *Tetrahedron* **1994**, *50*, 9643. (b) Kelly, T. R.; Garcia, A.; Lang, F.; Walsh, J. J.; Bhaskar, K. V.; Boyd, M. R.; Goetz, R.; Keller, P. A.; Walter, R.; Bringmann, G. *Tetrahedron Lett.* **1994**, *35*, 7621. (c) Hoye, T. R.; Chen, M.; Mi, L.; Priest, O. P. *Tetrahedron Lett.* **1994**, *35*, 8747.

(3) Hallock, Y. F.; Manfredi, K. P.; Blunt, J. W.; Cardellina, J. H., II; Schaeffer, M.; Gulden, K.-P.; Bringmann, G.; Lee, A. Y.; Clardy, J.; Francois, G.; Boyd, M. R. *J. Org. Chem.* **1994**, *59*, 6349.

(4) Bringmann, G.; Goetz, R.; Keller, P. A.; Walter, R.; Henschel, P.; Schaeffer, M.; Stablein, M.; Kelly, T. R.; Boyd, M. R. *Heterocycles* **1994**, *39*, 503.

(5) For a review, see: Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(6) For a review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(7) For a review, see: Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

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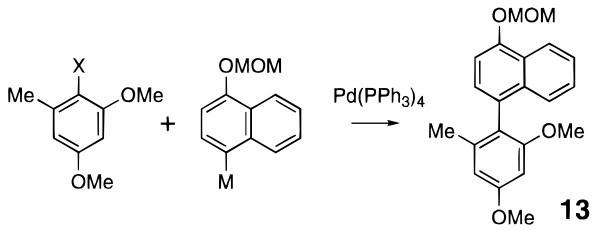
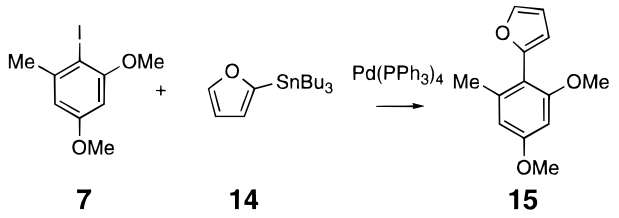
Table 1. Biaryl Coupling Reactions of 2,6-Disubstituted Phenyl Halides 6 and 7 with Metallated Naphthalenes 9−12

	Ar-X	Ar'-M	Method[a]	Yield[b] (%)
				**13**
1	**6** X = Br	**9** M = $SnBu_3$	A	0[c]
2	**7** X = I	**9** M = $SnBu_3$	A	0[c]
3	**6** X = Br	**10** M = $B(OH)_2$	B	56
4	**7** X = I	**10** M = $B(OH)_2$	B	79
5	**6** X = Br	**12** M = ZnCl	C	16[c]
6	**7** X = I	**12** M = ZnCl	C	50

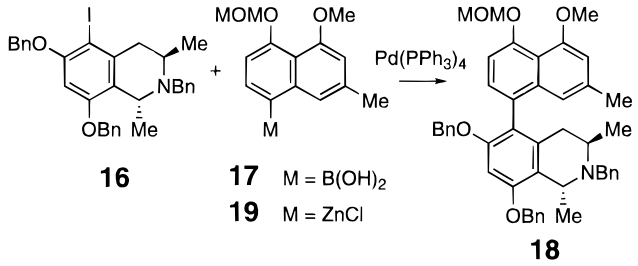
[a] Method A: ArX (0.1 M), Ar′$SnBu_3$ (2 equiv), $Pd(PPh_3)_4$ (10 mol %), PhMe, 110 °C. Method B: ArX (0.1 M), Ar′$B(OH)_2$ (2 equiv), $Pd(PPh_3)_4$ (10 mol %), PhMe, aqueous $NaHCO_3$, 110 °C. Method C: Ar′Li and $ZnCl_2$ in THF (−78 °C to rt) to ArX (0.2 M) and $Pd(PPh_3)_4$ (10 mol %) in THF, reflux. [b] Unless otherwise noted, yields are for isolated material following chromatograhpy on silica gel. [c] Extrapolated from GC/MS data.

iodide can be efficiently processed through the catalytic cycle when there is a sufficiently reactive (in this case, unhindered) arylmetal species present to capture the intermediate arylpalladium iodide. It was not clear at this stage whether the aryl bromide **6** was not capable of supporting the oxidative addition step or whether the resulting arylpalladium bromide was insufficiently reactive to continue the catalytic cycle.



7 **14** **15**

In light of these results, we turned to the Suzuki coupling reaction (entries 3 and 4 in Table 1). The boronic acid **10** was prepared from **8** by standard procedures. The crude boronic acid was a brown oil, whose proton NMR spectrum suggested the presence of several species. Consequently for the coupling reactions described here, 2 equiv of this crude boronic acid was routinely used. For characterization, the boronate ester **11** was prepared in 44% yield (after chromatographic purification) from **10** by being refluxed with 2,2-dimethyl-1,3-propanediol in toluene. Palladium-catalyzed Suzuki coupling reactions were then performed. A mixture of bromide **6** or iodide **7** and 2 equiv of the crude boronic acid **10**, 10 mol % of $Pd(PPh_3)_4$ in toluene (0.1 M), and an equal volume of saturated $NaHCO_3$ was heated at 110 °C for 16 h in a sealed culture tube under N_2 (method B). The desired coupled product **13** was isolated in 56% yield when **6** was used as starting material, while a 79% yield was obtained when **7** was the starting material. These encouraging results indicated that the Suzuki coupling conditions would work for this system. They also showed that the aryl bromide **6** was sufficiently reactive toward oxidative addition by palladium to be useful if a sufficiently reactive arylmetal partner was present. When these conditions were employed in our michellamine synthesis,[2c] we were delighted to observe the cross-coupling of iodide **16** with boronic acid **17**, which reproducibly provided a mixture of atropisomeric naphthylisoquinolines **18** in 65−85% yield in a 5:4 ratio. These conditions were also successfully applied in the synthesis of korupensamine C and *ent*-korupensamine D.[8]



16 **17** M = $B(OH)_2$ **19** M = ZnCl **18**

Recently we have investigated some relevant Negishi coupling reactions as well (entries 5 and 6). We were interested in this approach since the zinc compounds could be generated from the corresponding aryl bromides and then directly used as nucleophiles in the coupling reactions without handling of the arylmetal intermediates. Thus, the zinc reagent **12** was prepared from **8** by metal−halogen exchange with *n*-BuLi in THF, followed by reaction with $ZnCl_2$. The general procedure we studied for the biaryl coupling arylzinc species was as follows (method C): a THF solution of **12** (0.13 M) was added to a solution of aryl halide (0.2 M) and 5 mol % of $Pd(PPh_3)_4$ in THF. The resulting mixture was heated at 65 °C in a sealed culture tube under N_2. For couplings with the naphthylzinc reactant **12,** the aryl bromide **6** was considerably less reactive than the corresponding iodide **7**. After 20 h, reaction of the bromide **6** had proceeded to less than 20% conversion to biaryl product **13** (GC/MS). In contrast the coupling of aryl iodide **7** had proceeded to give **13** to a large extent even at room temperature (∼50% in 20 h) and to completion at 65 °C after 5 h, which resulted in a 50% yield of **13**. We then prepared the aryl zinc reagent **19** from its corresponding bromide and coupled it with the iodide **16**. The atropisomers of **18** were isolated in 53% yield under these conditions.

In conclusion, Pd^0-mediated cross-coupling reactions to construct the highly hindered biaryl bond present in various model systems relevant to korupensamine and michellamine synthesis were studied. Several different arylmetal systems were compared. No coupled product was observed under the Stille (Sn) conditions. Suzuki (B) coupling worked well for the desired system and has been used in the natural product syntheses. Comparable yields have now been obtained with the Negishi (Zn) coupling, where isolation of the intermediate zinc reagents is unnecessary.

Experimental Section

Method A. In a screw-capped culture tube were placed aryl halide (0.1 M), 2 equiv of aryl stannane, and 10 mol % of $Pd(PPh_3)_4$ in toluene. The reaction mixture was sealed under N_2

(8) (a) Hoye, T. R.; Mi, L. *Tetrahedron Lett.* **1996**, *37*, 3097. (b) Hoye, T. R.; Chen, M. *Tetrahedron Lett.* **1996**, *37*, 3099.

and heated to 110 °C for 20 h and then cooled to room temperature. The product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel.

Method B. The procedure is the same as method A except that the reaction mixture contains aryl halide (0.1 M), 2 equiv of crude aryl boronic acid, 10 mol % of $Pd(PPh_3)_4$ in toluene, and an equal volume of saturated $NaHCO_3$.

Method C. To a stirred solution of aryl bromide in THF (0.2 M) at −78 °C under N_2 was added 1.1 equiv of *n*-BuLi. The resulting mixture was stirred for 10 min. A solution of $ZnCl_2$ in THF (0.5 M) was then added. The reaction mixture was stirred for another 10 min and then warmed to room temperature and stirred for 10 min. This solution was added to a solution of aryl halide (0.2 M) and 5 mol % of $Pd(PPh_3)_4$ in THF. After the addition the mixture was heated under N_2 to 65 °C until TLC showed that no starting aryl halide remained. The reaction mixture was then quenched by addition of saturated $NaHCO_3$ and extracted with Et_2O. The rest of the procedure is the same as method A.

4-Bromo-1-(methoxymethoxy)naphthalene (9). To a stirred solution of 4-bromo-1-naphthol (**8**, 2.18 g, 9.77 mmol) and *i*-Pr_2NEt (15.0 mL, 11.1 g, 86.3 mmol) in 50 mL of THF at 0 °C under N_2 was added $MeOCH_2Cl$ (1.5 mL, 1.6 g, 20 mmol). The resulting mixture was stirred for 2 h at 0 °C and then warmed to room temperature and stirred for another 24 h. The reaction mixture was quenched by addition of saturated NH_4Cl. The mixture was extracted with Et_2O. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by MPLC (hexanes:EtOAc9:1) to yield 2.55 g (98%) of **9** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.28 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.61 (ddd, J = 7.0, 7.0 and 1.5 Hz, 1H), 7.53 (ddd, J = 7.0, 7.0 and 1.5 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 5.37 (s, 2H), and 3.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.4, 132.3, 129.3, 127.5, 126.9, 126.8, 125.9, 122.1, 114.3, 108.3, 94.6, and 56.1; LRMS (EI) m/z 268 (M^+, 8) and 266 (M^+, 9). Anal. Calcd for $C_{12}H_{11}BrO_2$: C, 53.96; H, 4.15. Found: C, 54.20; H, 4.25.

4-(Tri-*n*-butylstannyl)-1-(methoxymethoxy)naphthalene (10). To a stirred solution of **8** (160 mg, 0.60 mmol) in THF (10 mL) at −78 °C under N_2 was added *n*-BuLi (0.40 mL of a 2.0 M solution in hexanes, 0.80 mmol). The resulting mixture was stirred for 10 min. Bu_3SnCl (0.24 mL, 0.89 mmol) was added. The reaction mixture was stirred for another 10 min at −78 °C, warmed to room temperature, and stirred for 10 min. The reaction was quenched by addition of saturated $NaHCO_3$. The mixture was extracted with Et_2O. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated. The residue was purified by MPLC (hexanes:EtOAc 19:1) to give **10** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35−8.32 (m, 1H), 7.75−7.72 (m, 1H), 7.54−7.48 (m, 3H), 7.08 (d, J = 7.5 Hz, 1H), 5.40 (s, 2H), 3.55 (s, 3H), 1.59−1.49 (m, 6H), 1.40−1.28 (m, 6H), 1.20−1.15 (m, 6H), and 0.88 (t, J = 7.2 Hz, 9H).

Boronate Ester 11. To a stirred solution of **9** (1.85 g, 6.93 mmol) in THF (30 mL) at −78 °C under N_2 was added *n*-BuLi (3.1 mL of a 2.5 M solution in hexanes, 7.7 mmol). The resulting mixture was stirred for 15 min. A solution of $B(OMe)_3$ (1.6 mL, 1.5 g, 14 mmol) of in THF (30 mL) was then added. The reaction mixture was stirred for another 15 min, warmed to room temperature, and stirred for 2 h. The reaction mixture was quenched by addition of saturated NH_4Cl. The reaction mixture was diluted with Et_2O, washed with H_2O and brine, dried over $MgSO_4$, and concentrated to yield 1.6 g (∼100%) of crude boronic acid **10** as a brown oil. This material was used routinely for coupling reactions without further purification.

For characterization, boronate ester **11** was prepared as follows: the crude boronic acid **10** (1.6 g) and 2,2-dimethyl-1,3-propanediol (0.55 g, 5.3 mmol) were dissolved in 50 mL of toluene. The mixture was heated to reflux for 3 h. The solvent was then removed under reduced pressure. The residue was taken up in hexanes (3 × 5 mL); a hexanes-insoluble white solid was discarded. The combined hexanes layers were concentrated. The residue was purified by flash chromatography on silica gel (hexanes:EtOAc 9:1) to yield 0.92 g (44%) of **11** as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.84 (d, J = 8.1 Hz, 1H), 8.36 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.53 (m, 2H), 7.11 (d, J = 7.8 Hz, 1H), 5.43 (s, 2H), 3.88 (s, 4H), 3.56 (s, 3H), and 1.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.9, 138.0, 135.2, 128.1, 126.3, 125.6, 124.6, 121.8, 106.7, 94.4, 72.3, 56.1, 31.6, and 21.8; LRMS (EI) m/z 300 (M^+, 40). Anal. Calcd for $C_{17}H_{21}BO_4$: C, 68.03; H, 7.05. Found: C, 67.95; H, 6.89.

4-(2,4-Dimethoxy-6-methylphenyl)-1-(methoxymethoxy)naphthalene (13). Compound **13** was obtained by methods B and C after purification by column chromatography (hexanes:EtOAc 9:1) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.32 (dd, J = 8.5 and 1.0 Hz, 1H), 7.47−7.43 (m, 1H), 7.38−7.35 (m, 2H), 7.17 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 2.5 Hz, 1H), 6.46 (d, J = 2.5 Hz, 1H), 5.44 (d, J = 6.0 Hz, 1H), 5.41 (d, J = 6.0 Hz, 1H), 3.87 (s, 3H), 3.59 (s, 3H), 3.58 (s, 3H), and 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.7, 158.8, 152.1, 139.7, 133.5, 128.9, 127.6, 126.1, 126.0, 125.7, 124.9, 122.0, 121.4, 107.6, 106.2, 96.1, 94.8, 56.3, 55.7, 55.3, and 20.5; LRMS (EI) m/z 338 (M^+, 100). Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.89; H, 6.78.

2-(2-Furyl)-3,5-dimethoxytoluene (15). Method A was used to prepare compound **15** from **7** and **14**. The product was obtained after purification by column chromatography (hexanes:EtOAc 19:1) in 90% yield as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 (dd, J = 2.0 and 0.5 Hz, 1H), 6.47 (d, J = 3.5 and 1.5 Hz, 1H), 6.40 (d, J = 2.5 Hz, 1H), 6.37−6.36 (m, 2H), 3.81 (s, 3H), 3.74 (s, 3H), and 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.6, 159.2, 141.4, 140.7, 113.2, 110.5, 109.9, 106.8, 105.2, 96.2, 55.8, 55.3, and 21.1; LRMS (EI) m/z 218 (M^+, 100). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.47; H, 6.43.

5-[(1*R*,3*R*)-2-Benzyl-6,8-bis(benzyloxy)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl]-1-methoxy-8-(methoxymethoxy)-3-methylnaphthalene (18). Compound **18**, prepared by methods B and C, was purified by MPLC (hexanes:EtOAc 3:1, with 3% Et_3N) as a mixture of atropisomers, **18-*S*** and **18-*R***, with a 5:4 ratio. ^{1}H NMR (500 MHz, $CDCl_3$) for **18-*S*** (from the mixture of **18-*S*** and **18-*R***): δ 7.39−6.90 (m, 17H), 6.77 (s, 1H), 6.69 (s, 1H), 6.53 (s, 1H), 5.31 (s, 2H), 5.02 (s, 2H), 4.87 (d, J = 12.5 Hz, 1H), 4.81 (d, J = 12.5 Hz, 1H), 4.12 (q, J = 6.5 Hz, 1H), 3.98 (s, 3H), 3.72 (d, J = 14.5 Hz, 1H), 3.65 (s, 3H), 3.37 (ddq, J = 11.5, 4.0, and 6.5 Hz, 1H), 3.30 (d, J = 14.5 Hz, 1H), 2.36 (s, 3H), 2.22 (dd, J = 17.5 and 4.0 Hz, 1H), 2.00 (dd, J = 17.5 and 11.5 Hz, 1H), 1.41 (d, J = 6.5 Hz, 3H), and 1.01 (d, J = 6.5 Hz, 3H). ^{1}H NMR (500 MHz, $COCl_3$) for **18-*R*** (from the mixture of **18-*S*** and **18-*R***) δ 7.39−6.90 (m, 17H), 6.86 (s, 1H), 6.70 (s, 1H), 6.51 (s, 1H), 5.31 (s, 2H), 5.03 (d, J = 12.0 Hz, 1H), 4.97 (d, J = 12.0 Hz, 1H), 4.86 (d, J = 12.5 Hz, 1H), 4.81 (d, J = 12.5 Hz, 1H), 4.11 (q, J = 6.5 Hz, 1H), 3.98 (s, 3H), 3.77 (d, J = 14.5 Hz, 1H), 3.65 (s, 3H), 3.37 (ddq, J = 14.0, 4.0, and 6.5 Hz, 1H), 3.35 (d, J = 14.0 Hz, 1H), 2.36 (s, 3H), 2.25 (dd, J = 17.0 and 14.0 Hz, 1H), 1.92 (dd, J = 17.0 and 4.0 Hz, 1H), 1.39 (d, J = 6.5 Hz, 3H), and 1.05 (d, J = 6.5 Hz, 3H). HRMS (FAB): calcd for $C_{46}H_{48}NO_5$ $(M + H)^+$ 694.3532, found 694.3546.

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