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First total synthesis of the 7,6′-coupled antifungal naphthylisoquinoline alkaloid dioncophylline B☆

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Dedicated to Professor T. R. Govindachari, on the occasion of his 85th birthday

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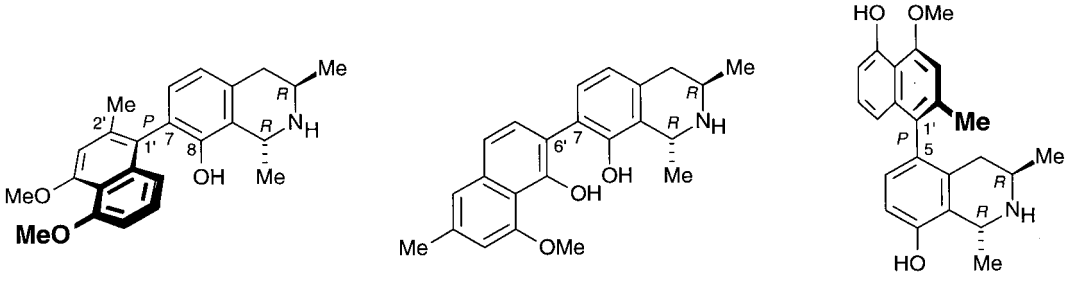
Abstract—The first total synthesis of the antimalarial alkaloid dioncophylline B (**2**) from *Triphyophyllum peltatum* (Dioncophyllaceae), and thus the first preparation of a 7,6′-coupled naphthylisoquinoline, is described. Key steps within this synthesis are the *ortho*-functionalization of the MOM-protected naphthalene and isoquinoline moieties **14** and **7** by directed *ortho*-metalation, with subsequent stannylation of the naphthalene part and bromination of the isoquinoline portion, and the regioselective intermolecular Stille coupling reaction of these building blocks. The presented synthesis opens the way for the preparation of further 7-coupled compounds of this class of alkaloids.

1. Introduction

The naphthylisoquinoline alkaloids[2,3] are structurally diverse natural products from tropical Ancistrocladaceae and Dioncophyllaceae plants, exhibiting a broad spectrum of bioactivities, like antimalarial,[4] anti-HIV,[5] antitrypanosomal,[6] and fungicidal[7] properties. For this reason and because of the structural variety arising from the different ways by which the isoquinoline moiety and the naphthalene portion are linked to each other, from the substitution patterns, the hydrogenation degrees, and the configurations at the various stereogenic elements, these secondary metabolites constitute challenging synthetic goals.[2,8–11] As an example, dioncophylline A (**1**, see Fig. 1),[12] an insect antifeedant[13,14] and molluscicidal[15] alkaloid from *Triphyophyllum peltatum* (Hutch. and Dalz.) Airy Shaw (Dioncophyllaceae), has its biaryl axis between C-7 of the isoquinoline part and C-1′ of the naphthalene half. By contrast, dioncophyllines B[16] (**2**) and C[17] (**3**), which have been isolated from the same plant and exhibit strong fungicidal[7] and in vivo antimalarial[18] activities, respectively, are 7,6′- and 5,1′-coupled. Depending on the degree of steric hindrance at the biaryl axis between the naphthalene moiety and the isoquinoline portion, most of the naphthylisoquinoline alkaloids show the phenomenon of axial chirality, giving rise to configurationally stable atropisomeric forms, as is the case for **1** and **3**. Dioncophylline B (**2**), however, with its only two small hydroxy functions next to the biaryl



1 2 3

Figure 1. Three bioactive naphthylisoquinoline alkaloids: dioncophyllines A (**1**), B (**2**), and C (**3**).

☆ Acetogenic Isoquinoline Alkaloids, Part 147.[1]

Keywords: dioncophylline B; naphthylisoquinoline alkaloids; total synthesis; cross coupling; directed *ortho*-metalation.
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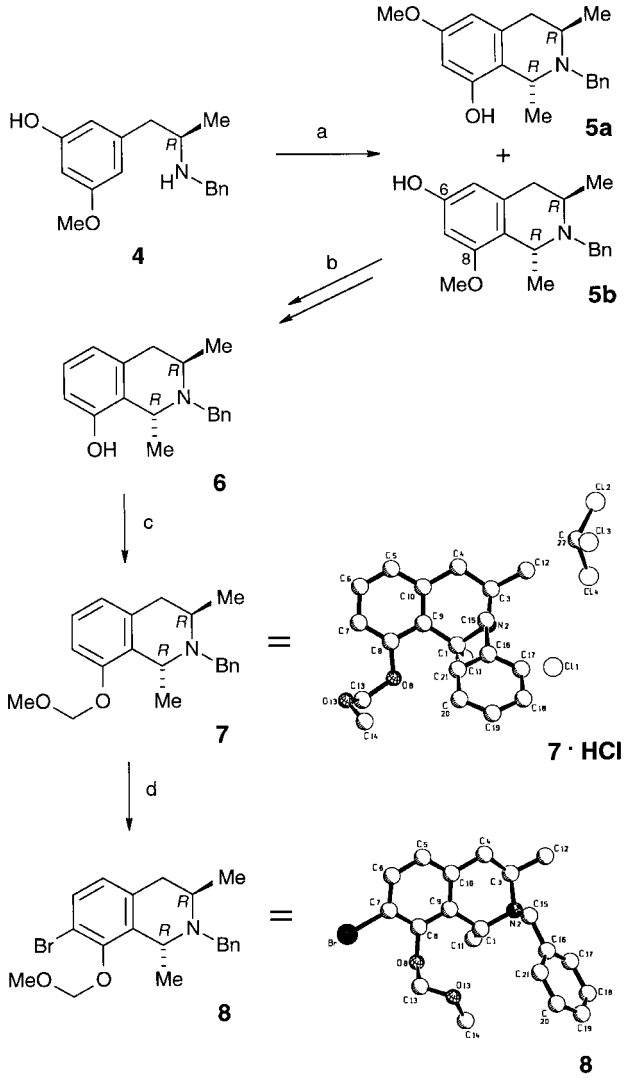
axis, is configuratively unstable and undergoes rapid atropisomeric interconversion at room temperature.[16] Most of the numerous naphthylisoquinoline alkaloids that have meanwhile been synthesized (among them **1**),[19,20] have been built up by our 'lactone method'.[21] This technique relies on the intramolecular coupling of the ester-type pre-linked aromatic moieties and subsequent atroposelective ring cleavage of the resulting—mostly still configurationally unstable—biaryl lactones. A fundamental precondition for the method is, however, the presence of an oxygen function next to the axis (e.g. 8-OH in **1**) and a C_1-containing group (e.g. 2′-CH_3 in **1**), as bridge heads for the lactone construction—but the latter prerequisite is not fulfilled for **2**. Although the lactone method has already proved to be flexible enough to provide efficient synthetic access even to compounds that do not correspond to these structural requirements (e.g. with no *ortho*-oxygen function next to the axis as in **3**,[8] or with the C_1-unit being 'cryptic', as part of the naphthalene system),[11] it here seemed more favorable to build up the 7,6′-coupled target molecule dioncophylline B (**2**) by an *intermolecular* coupling reaction. The otherwise remarkable properties of the lactone method—to overcome even highest steric hindrance in the coupling step with mostly excellent chemical and optical yields—were not really required for the preparation of **2**, with its small *ortho*-substituents next to the axis and thus configurational instability. In this paper, we report on the first total synthesis of dioncophylline B (**2**), thus relying on an intermolecular coupling step, based on the—to the best of our knowledge—first *double* 'Directed *ortho*-Metalation (DoM)[22]→cross coupling' approach for the synthesis of biaryl alkaloids.

2. Results and discussion

The intended intermolecular coupling strategy to dioncophylline B (**2**) required an appropriate functionalization of the two molecular moieties. Thus, a 'DoM→cross coupling' sequence was chosen to achieve a short and convergent synthetic access to **2**. The DoM strategy has been established as a valuable tool for the regioselective introduction of substituents into aromatic compounds.[22] It takes advantage of the complexing activity of 'Directed Metalation Groups' (DMG's) like carbamate and methoxymethoxy (MOM) functions.[22] These groups direct metals (e.g. lithium) into the adjacent *ortho* position; the resulting lithiated arene may then be trapped using a broad range of electrophiles. For the synthesis of **2**, we chose the MOM group[23] as the DMG and, simultaneously, protecting group for both, the naphthalene and the isoquinoline building blocks, since it is strongly *ortho*-directing and can easily be introduced and later removed under mild acidic conditions.[24] According to previous experience during our first total synthesis of the structurally related korupensamines,[25] we decided to use the isoquinoline as the brominated starting material and the naphthalene as the stannylated reaction partner for the Stille coupling. The enantio- and diastereomerically pure isoquinoline building block **6** (see Scheme 1) was prepared according to a synthesis elaborated earlier,[26] but with an additional significant improvement in the resolution of the two regioisomeric Pictet–Spengler products **5a** and **5b** obtained from **4**. The desired isomer **5b**, hitherto usually deliberated from **5a** by repeated column chromatography,[26] has now been purified most conveniently, by precipitation of its methanesulfonate salt. The following removal of the 6-hydroxy and the 8-*O*-methyl groups was performed as reported earlier.[26] Introduction of the MOM group into **6**, by reaction with (chloromethoxy)methane,[27] gave **7**. Interestingly, **7** crystallizes from $CHCl_3$ with 1 equiv. of the solvent, as seen by an X-ray structure analysis (see Scheme 1). The anticipated DoM reaction on **7** by *n*-butyllithium/*N*,*N*,*N*′,*N*′-tetramethylethylendiamine (TMEDA), with subsequent careful treatment of the metalated intermediate with 1,2-dibromotetrachloroethane at −78°C, gave the desired building block **8** in good yield and excellent regioselectivity: By HMBC investigations (not shown) and by an X-ray structure analysis of **8** (see Scheme 1), the bromo substituent was found to be located in the required 7-position of the isoquinoline, and no regioisomeric or overreacted halogenation products were detected. If, however, the halogen source was added at room temperature, inseparable mixtures of the corresponding

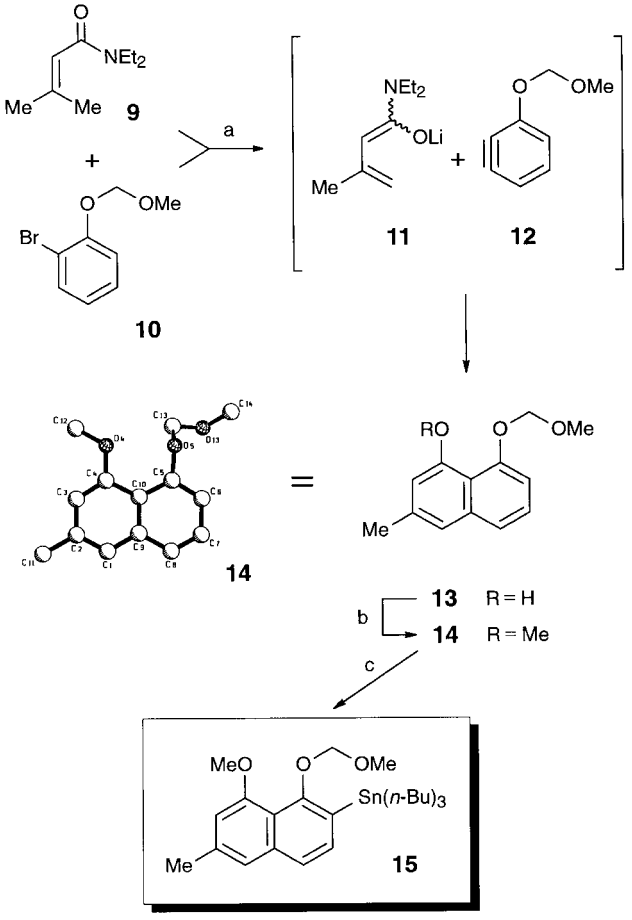


Scheme 1. Synthesis of the isoquinoline building block **8**. *Reagents and conditions*: (a) CH_3CHO, *i*PrOH, H_2O, rt, 92%; (b) (i), crystallization of **5b**·$MeSO_3H$, (ii), $(F_3CSO_2)_2O$, DABCO, 94%; (iii), $Pd(OAc)_2$, $(n\text{-}Bu)_3N$, HCOOH, 93%, (iv), EtSNa, DMF, reflux, 85%; (c) NaH, THF, MOMCl, 87%; (d) *n*-BuLi, TMEDA, petroleum ether, −78°C, then $(CBrCl_2)_2$, 82%.

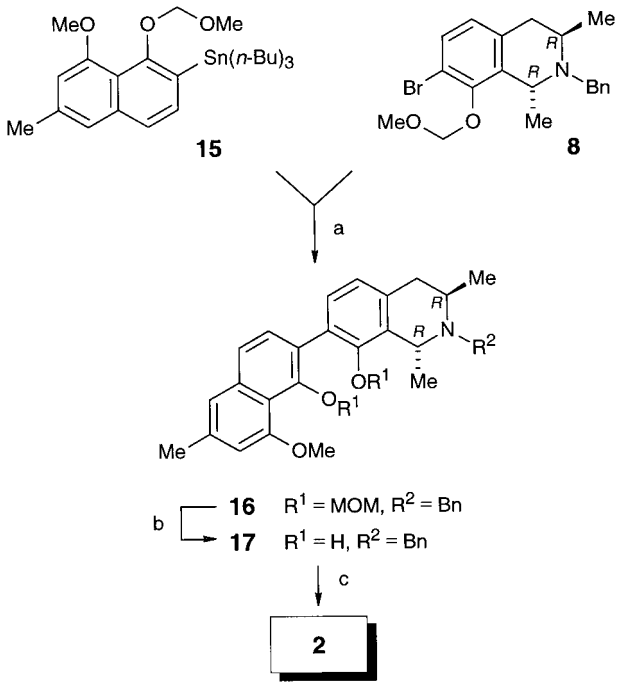
bromo and chloro derivatives resulted. The now synthetically available 7-functionalized isoquinoline is a new valuable building block not only for the synthesis of **2** as described here, but also for the preparation of further 7-coupled naphthylisoquinolines and their—potentially bioactive—derivatives.

For the preparation of the naphthalene, a Diels–Alder procedure according to Watanabe[28] was selected, starting with the amide enolate **11** (generated in situ from the acrylic amide **9**,[29] see Scheme 2) and the aryne **12** (from the MOM-protected 2-bromophenol **10**, likewise prepared in situ).[30] The transformation delivered the appropriately substituted building block **13** in only one step. Its methyl ether **14**, whose structure was confirmed by X-ray crystallography, was lithiated and subsequently quenched with tri-*n*-butyltin chloride to give stannane **15**.

With the two coupling precursors now in hand, Stille coupling[31] of **15** (generated in situ) with **8** using bis(triphenylphosphine)palladium(II) chloride as the catalyst, yielded the desired, still protected naphthylisoquinoline **16** in a quite satisfying yield (see Scheme 3).[32] Acid-catalyzed removal of the two MOM groups and hydrogenolytic cleavage of the benzyl function eventually afforded dioncophylline B (**2**), which was found to be identical in all respects with natural material from *T. peltatum*.[16]



Scheme 2. Preparation of the specifically stannyl-activated naphthalene **15**. *Reagents and conditions*: (a) LiN(*i*Pr)(C_6H_{11}), THF, −78°C, 32%; (b) K_2CO_3, Me_2SO_4, 88%; (c) *n*-BuLi, TMEDA, petroleum ether, −50°C, then $(n\text{-Bu})_3SnCl$.



Scheme 3. Completion of the synthesis of dioncophylline B (**2**). *Reagents and conditions*: (a) $Pd(PPh_3)_2Cl_2$, PPh_3, CuBr, LiCl, DMF, 135°C, 56% from **14**; (b) HCl, *i*PrOH, THF, reflux, 91%; (c) Pd^0, HCOOH, MeOH, 40°C, 68%.

In summary, the highly convergent synthesis of dioncophylline B (**2**) described here, constitutes the first synthetic access to a 7,6′-coupled naphthylisoquinoline alkaloid at all. Especially with regard to the promising antimalarial activity of **2** and of its likewise active dimer,[33] the now possible synthesis of further, structurally simplified 7-coupled derivatives is a rewarding goal. This work is in progress.

3. Experimental

3.1. General

Melting points were measured on a Reichert-Jung Thermovar hot-plate and are uncorrected. IR spectra were taken on a Perkin–Elmer 1420 infrared spectrophotometer and are reported in wave numbers (cm^{-1}). NMR spectra were recorded with Bruker AC 200, AC 250, and DMX 600 spectrometers. The chemical shifts δ are given in parts per million (ppm) with the proton signals in the deuterated solvent as internal reference for ^1H and ^{13}C NMR. Coupling constants, *J*, are reported in Hertz. The mass spectra were obtained on Finnigan MAT 8200 and MAT 90 mass spectrometers at 70 eV in the EI mode. Silica gel (60–200 mesh, Merck) was used for column chromatography, and precoated silica gel 60 F_{254} plates (Merck) for TLC. Spots were detected under UV light. Dioncophylline B (**2**) was available by isolation from *T. peltatum* (Dioncophyllaceae). Compounds **6**[26] (except for the improvement

described below), **9**,[29] **10**,[30] and **13**[28] were prepared as published previously.

3.1.1. Separation of (1*R*,3*R*)-*N*-benzyl-8-hydroxy-6-methoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (5a) and (1*R*,3*R*)-*N*-benzyl-6-hydroxy-8-methoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (5b). 2 ml (2.96 g, 30.8 mmol) of methanesulfonic acid were added dropwise to a solution of 5 g (16.8 mmol) mixture of **5a** and **b** in 100 ml Et_2O prepared according to Ref. 26 until there was no further precipitation. After filtration, the solid was dried in vacuo and dissolved again in acetone. A few seconds later a white amorphous solid was formed, which was filtered and rinsed with acetone. The solid consisted of 4.36 g (11.1 mmol) of pure **5b** methanesulfonate, which was transformed to the free base (3.27 g, 11.0 mmol) by treatment with NH_3. The supernatant liquid contained a mixture of about 80% **5a** and 20% **5b**. For physical and spectroscopic data see Ref. 26.

3.1.2. (1*R*,3*R*)-*N*-Benzyl-8-(methoxymethoxy)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (7). A mixture of 200 mg (749 μmol) **6**[26] in 5 ml dry THF and 26.9 mg (1.12 mmol) NaH was stirred for 30 min at room temperature. After addition of 187 μl (1.12 mmol) of a 6 M solution of (chloromethoxy)methane prepared according to Ref. 27, the suspension was filtered and the solid was rinsed with Et_2O. Column chromatography of the filtrate on deactivated (5% NH_3) silica gel afforded 202 mg (650 μmol, 87%) of **7** as a bright yellow oil; its hydrochloride was crystallized from $CHCl_3$/petroleum ether: mp 228–229°C; $[\alpha]_D^{25}$=+10.0 (c=1.01 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 2900 (s, C–H), 2520 (m), 1570 (s), 1438 (s), 1245 (s), 1135 (s), 1040 (s), 1020 (s), 1000 (s), 935 (m), 910 (m), 740 (s), 690 (m); ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.29 (d, J=6.7 Hz, 3H, 3-CH_3), 1.35 (d, J=6.7 Hz, 3H, 1-CH_3), 2.65 (d, J=6.9 Hz, 2H, 4-CH_2), 3.28 (d, J=14.1 Hz, 1H, NC*H*HPh), 3.35 (s, 3H, OCH_3), 3.54 (m, 1H, 3-H), 3.86 (d, J=14.0 Hz, 1H, NCH*H*Ph), 4.00 (q, J=6.7 Hz, 1H, 1-H), 5.12 (s, 2H, OCH_2O), 6.77 (d, J=7.6 Hz, 1H, 5-H), 6.88 (d, J=7.3 Hz, 1H, 7-H), 7.10 (dd, J=7.9 Hz, J=7.9 Hz, 1H, 6-H), 7.20–7.42 (m, 5H, Ph); ^{13}C NMR (63 MHz, $CDCl_3$): δ=19.67 (3-CH_3), 20.00 (1-CH_3), 31.91 (C-4), 45.62 (C-3), 49.73 (NCH_2Ph), 51.39 (C-1), 55.90 (OCH_3), 93.86 (OCH_2O), 110.84 (C-7), 122.20 (C-5), 126.32 (C-6), 126.41 (Ph), 128.05 (Ph), 128.48 (Ph), 128.56 (Ph), 136.29 (C-9), 141.19 (C-10), 154.77 (C-8). MS: m/z (%)=311 (1) $[M]^+$, 296 (44) $[M-CH_3]^+$, 280 (1) $[M-OCH_3]^+$, 266 (3) $[M-CH_2OCH_3]^+$, 252 (16), 91 (100) $[PhCH_2]^+$, 45 (66) $[CH_2OCH_3]^+$.

3.1.3. (1*R*,3*R*)-*N*-Benzyl-7-bromo-8-(methoxymethoxy)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (8). 96.4 μl (145 μmol) of a 1.5 M solution of *n*-BuLi in hexane and 11.2 mg (14.4 μl, 96.4 μmol) TMEDA were added at 0°C to a stirred solution of 30.0 mg (96.4 μmol) **7** in 2 ml dry petroleum ether. After warming to 10°C stirring was continued for 1 h. The resulting black suspension was cooled to −78°C and treated with 47.1 mg (145 μmol) $(CBrCl_2)_2$. After allowing the mixture to warm up to room temperature and removal of the solvent in vacuo, purification of the product was achieved by column chromatography on deactivated (5% NH_3) silica gel with CH_2Cl_2/methanol as the eluent, affording 31.0 mg (79.4 μmol, 82%) of **8**. The product was crystallized from methyl *tert.*-butyl ether/petroleum ether: mp 118–119°C; $[\alpha]_D^{25}$=−87.7° (c=1.02 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 2930 (s, C–H), 1440 (s), 1420 (s), 1360 (m), 1150 (s), 1070 (s), 975 (s), 910 (s), 790 (m), 730 (m), 690 (m); ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.30 (d, J=6.7 Hz, 3H, 3-CH_3), 1.36 (d, J=6.9 Hz, 3H, 1-CH_3), 2.60 (d, J=8.0 Hz, 2H, 4-CH_2), 3.00 (s, 3H, OCH_3), 3.30 (d, J=14.0 Hz, 1H, NC*H*HPh), 3.49 (q, J=6.7 Hz, 1H, 3-H), 3.87 (d, J=14.3 Hz, 1H, NCH*H*Ph), 4.05 (q, J=6.8 Hz, 1H, 1-H), 4.80 (d, J=5.9 Hz, 1H, OC*H*HO), 4.99 (d, J=5.9 Hz, 1H, OCH*H*O), 6.78 (d, J=8.2 Hz, 1H, 5-H), 7.20–7.44 (m, 5H, Ph), 7.32 (d, J=8.3 Hz, 1H, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=19.73 (3-CH_3), 19.94 (1-CH_3), 31.66 (C-4), 45.43 (C-3), 49.71 (NCH_2Ph), 52.09 (C-1), 56.82 (OCH_3), 99.64 (OCH_2O), 114.06 (C-7), 126.31 (C-5), 126.59 (Ph), 128.14 (Ph), 128.41 (Ph), 130.56 (C-6), 135.54 (C-9), 135.99 (C-10), 140.75 (Ph), 152.79 (C-8); MS: m/z (%)=389/391 (1/1) $[M]^+$, 374/376 (16/16) $[M-CH_3]^+$, 344/346 (1/2) $[M-CH_2OCH_3]^+$, 265 (9) $[M-Br-CH_2OCH_3]^+$, 91 (100) $[C_7H_7]^+$, 45 (21) $[CH_2OCH_3]^+$. Anal. calcd for $C_{20}H_{24}BrNO_2$ (390.32): C, 62.36; H, 6.20; N, 3.59. Found: C, 62.86; H, 6.16; N, 3.58.

3.1.4. 4-Methoxy-5-(methoxymethoxy)-2-methylnaphthalene (14). To a solution of 1.00 g (4.59 mmol) **13**[28] in 15 ml dry acetone, 1.90 g (13.8 mmol) K_2CO_3 and 1.74 g (1.31 ml, 13.8 mmol) Me_2SO_4 were added. After 8 h refluxing, the mixture was treated with 4 ml concentrated NH_3 and again heated under reflux for 45 min. The crude product, after removal of the solvent in vacuo, was purified by column chromatography on silica gel with CH_2Cl_2/petroleum ether (50:50→100:0), yielding 938 mg (4.04 mmol, 88%) of **14** as a crystalline powder from methyl *tert.*-butyl ether/petroleum ether: mp 75–76°C; IR (KBr): $\tilde{\nu}$ 2940 (m, C–H), 1590 (m), 1570 (s), 1380 (m), 1370 (m), 1350 (m), 1270 (s), 1150 (s), 1120 (s), 1090 (s), 1030 (s), 960 (s), 940 (s), 840 (m), 760 (m); ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.46 (d, J=0.8 Hz, 3H, 2-CH_3), 3.61 (s, 3H, CH_2OCH_3), 3.96 (s, 3H, 5-OCH_3), 5.26 (s, 2H, OCH_2O), 6.68 (d, J=1.4 Hz, 1H, 3-H), 7.00 (dd, J=7.4 Hz, J=1.3 Hz, 1H, 6-H), 7.19 (br. s, 1H, 1-H), 7.31 (dd, J=7.8 Hz, J=7.8 Hz, 1H, 7-H), 7.40 (dd, J=8.2 Hz, J=1.2 Hz, 1H, 8-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ=21.81 (2-CH_3), 56.24 (4-OCH_3), 56.38 (CH_2OCH_3), 96.90 (OCH_2O), 107.71, 108.36 (C-3), 112.85 (C-6), 120.04 (C-1), 122.23 (C-8), 126.35 (C-7), 136.03, 137.56, 153.80, 156.38; MS: m/z (%)=232 (45) $[M]^+$, 202 (44) $[M-H_2CO]^+$, 186 (10) $[M-C_2H_6O]^+$, 159 (10), 129 (16), 128 (18), 115 (12), 45 (100) $[CH_2OCH_3]^+$. Anal. calcd for $C_{14}H_{16}O_3$ (232.28): C, 72.39; H, 6.94. Found: C, 72.49; H, 6.69.

3.1.5. (1*R*,3*R*)-*N*-Benzyl-7-[4′-methoxy-5′-(methoxymethoxy)-2′-methyl-6′-naphthyl]-8-(methoxymethoxy)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (16). After addition of 288 μl (434 μmol) of a 1.5 M solution of *n*-BuLi in hexane and 42.7 μl (33.5 mg, 288 μmol) TMEDA to a cooled (−50°C) suspension of 66.9 mg (288 μmol) of **14** in dry petroleum ether, the reaction mixture was allowed to warm up to 0°C over 2 h. The solution was again cooled to −70°C and was augmented by 157 μl (187 mg, 577 μmol) tri-*n*-butyltin chloride. After having reached

room temperature again, the mixture was hydrolyzed with 3 ml of saturated aqueous ammonium chloride and extracted several times with Et_2O. Drying of the combined organic layers with magnesium sulfate and removal of the solvent in vacuo afforded a colorless liquid, which was used for the coupling reaction without further purification. A mixture of 37.4 mg (95.5 μmol) **8**, 15.0 mg (57.3 μmol) PPh_3, 13.4 mg (19.1 μmol) $Pd(PPh_3)_2Cl_2$, 33.4 mg (788 μmol) dry LiCl, and 1.23 mg (8.60 μmol) CuBr was dried for 40 min at room temperature in vacuo and was subsequently dissolved in 5 ml dry DMF. The solution was heated to 135°C in a pre-heated bath. After 5 min (and after 30 min again) 1 ml of a solution of the stannane **15** in 2 ml dry DMF was added. When the reaction mixture had turned black (about 3 h), the solvent was removed in vacuo. Purification of the product by column chromatography on deactivated (5% NH_3) silica gel using CH_2Cl_2/methanol (100:0→99:1) as the eluent gave 29.1 mg (53.7 μmol, 56% based on **8**) **16** as an oil: $[\alpha]_D^{20}=+60.3°$ (c=0.25 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3400 (m, O–H), 2940 (m, C–H), 1610 (m), 1550 (m), 1440 (m), 1325 (m), 1145 (s), 1085 (m), 980 (s), 930 (m); ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.33 (d, J=6.6 Hz, 3H, 3-CH_3), 1.47 (d, J=6.8 Hz, 3H, 1-CH_3), 2.48 (d, J=0.4 Hz, 3H, 2′-CH_3), 2.75 (m, 5H, 4-H_{eq}, 4-H_{ax}, CH_2OCH_3), 2.92 (d, J=13.6 Hz, 1H, NC*H*HPh), 3.91 (d, $J\approx$14.0 Hz, 1H, NCH*H*Ph), 3.58 (m, 1H, 3-H), 3.96 (s, 3H, 4′-OCH_3), 4.10 (q, J=6.7 Hz, 1H, 1-H), 4.35 (d, J=5.9 Hz, 1H, OC*H*HO), 4.96 (d, J=5.4 Hz, 1H, OCH*H*O), 6.70 (s, 1H, 3′-H), 6.94 (d, J=7.8 Hz, 1H, 5-H), 7.18–7.50 (m, 9H, Ar–H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=19.76, 20.42, 21.79 (3-CH_3, 1-CH_3, 2′-CH_3), 31.87 (C-4), 45.52 (C-3), 49.73 (CH_2Ph), 51.91 (C-1), 56.00, 56.35 (4′-OCH_3, 2 CH_2OCH_3), 98.64 (OCH_2O), 100.85 (OCH_2O), 108.18 (C-3′, C-10′), 118.11 (C-6′, C-8′), 120.27 (C-1′), 121.84 (C-5), 123.47 (C-7), 126.43 (C-9), 128.11 (C-6 and Ph), 128.37 (Ph), 129.68 (Ph), 131.34 (C-7′), 135.21, 136.03, 137.18 (C-2′, C-9′, C-10), 141.08 (Ph), 150.41 (C-5′, C-8), 155.77 (C-4′); MS: m/z (%)=541 (0.5) $[M]^+$, 526 (100) $[M-CH_3]^+$, 482 (7) $[M-CH_3-C_2H_4O]^+$, 450 (12) $[M-CH_2Ph]^+$, 420 (14) $[M-CH_2Ph-2CH_3]^+$, 91 (15) $[CH_2Ph]^+$, 45 (5) $[CH_2OCH_3]^+$. Exact mass calcd for $C_{33}H_{36}NO_5$ $(M-CH_3)^+$ 526.2593. Found 526.2592.

3.1.6. (1*R*,3*R*)-*N*-Benzyl-7-(5′-hydroxy-4′-methoxy-2′-methyl-6′-naphthyl)-8-hydroxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (17). A solution of 20.0 mg (36.9 μmol) **16**, 500 μl 1N aqueous HCl and 500 μl isopropanol in 1 ml THF was refluxed for 45 min. Removal of the solvent in vacuo and subsequent column chromatography on deactivated silica gel using CH_2Cl_2/methanol (100:0→98:2) as the eluent yielded 15.3 mg (33.7 μmol, 91%) **17** as an amorphous solid: $[\alpha]_D^{20}=+88.0°$ (c=0.48 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3230 (s, O–H), 2940 (m, C–H), 1620 (m), 1565 (m), 1440 (m), 1385 (m), 1350 (s), 1315 (m), 1240 (m), 1135 (m), 1100 (m), 1020 (m); ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.31 (d, J=6.7 Hz, 3H, 3-CH_3), 1.46 (d, J=6.7 Hz, 3H, 1-CH_3), 2.49 (d, J=0.5 Hz, 3H, 2′-CH_3), 2.71 (m, 2H, 4-H_{eq} and 4-H_{ax}), 3.41 (d, J=14.3 Hz, 1H, NC*H*HPh), 3.58 (m, 1H, 3-H), 3.90 (d, J=14.4 Hz, 1H, NCH*H*Ph), 4.07 (s, 3H, 4′-OCH_3), 4.17 (q, J=6.8 Hz, 1H, 1-H), 6.69 (d, J=1.2 Hz, 1H, 3′-H), 6.74 (s, 1H, 1′-H), 6.83 (d, J=7.9 Hz, 1H, 5-H), 7.16 (d, J=7.8 Hz, 1H, 6-H), 7.21–7.46 (m, 7H, Ar–H), 10.32 (s, 1H, 5′-OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=19.69, 19.82, 21.91 (3-CH_3, 1-CH_3, 2′-CH_3), 32.17 (C-4), 45.83 (C-3), 49.96 (CH_2Ph), 52.21 (C-1), 56.37 (4′-OCH_3), 107.27 (C-3′), 112.99 (C-10′), 119.40 (C-6′), 119.66 (C-8′), 120.98 (C-1′), 121.29 (C-5), 123.78 (C-7), 126.30 (C-9), 128.05 (C-6 and Ph), 128.47 (Ph), 131.13 (C-7′), 135.72, 136.13, 136.28 (C-2′, C-9′, C-10), 141.50 (Ph), 149.14 (C-5′), 151.60 (C-8), 155.77 (C-4′); MS: m/z (%)=453 (1) $[M]^+$, 438 (100) $[M-CH_3]^+$, 423 (9) $[M-2CH_3]^+$, 219 (4) $[M-CH_3]^{2+}$, 91 (13) $[CH_2Ph]^+$. Exact mass calcd for $C_{29}H_{28}NO_3$ $(M-CH_3)^+$ 438.2069. Found 438.2071.

3.1.7. Dioncophylline B (2). A mixture of 12.4 mg (27.1 μmol) **17** in 1 ml dry methanol, 3.45 mg Pd^0, and 100 μl (82.0 mg, 1.78 mmol) HCOOH was stirred for 2 h at 40°C. After repeated extraction with CH_2Cl_2/water, the solvent of the combined organic layers was removed in vacuo, and the residue was resolved by column chromatography on deactivated (5% NH_3) silica gel using CH_2Cl_2/methanol 9:1, yielding 6.68 mg (18.4 μmol, 68%) **2**: $[\alpha]_D^{20}=-34.2°$ (c=0.12 in $CHCl_3$); Ref. 16 −37.6° (c=0.37 in $CHCl_3$). Exact mass calcd for $C_{22}H_{22}NO_3$ $(M-CH_3)^+$ 297.1600. Found 297.1596. All spectroscopic and physical data were in accordance with those published in the literature.[16]

3.2. Single-crystal X-ray diffraction analyses of 7, 8 and 14

All measurements of diffraction intensities were performed on a Bruker AXS P4 diffractometer with an incident beam graphite monochromator (MoKα radiation, λ=0.71073 Å) in ω-scan mode in the range of $1.75°<\theta<27.5°$.[34] The structures were solved by direct phase determination and refined by full-matrix anisotropic least-squares with the aid of the program SHELXTL-PLUS.[35] All non-hydrogen atoms were refined anisotropically. The hydrogen positions were calculated using a riding model and were considered fixed with isotropic thermal parameters in all refinements. Software used to prepare material for publication: SCHAKAL 88.[36]

3.2.1. Crystal data for 7. The crystal chosen for X-ray investigations was a clear colorless plate with the approximate dimensions 0.35×0.65×0.85 mm. $C_{20}H_{25}NO_2\cdot HCl\cdot CHCl_3$ (467.26 g mol^{-1}) crystallizes in the monoclinic system, space group $P2_1$, with a=13.2511 (9), b=7.3856 (6), c=13.527 (1) Å, β=118.479 (5)°, V=1163.7 (2) Å^3, Z=2, μ(MoKα)=0.53 mm^{-1}, and D_{calcd}=1.334 g cm^{-3}. The unit cell parameters were determined by least-squares refinement using 61 centered reflections within $12.6°<\theta<17.5°$. A total of 6033 reflections were collected in ω-scan mode to $2\theta_{max}=55°$ (h: −1→17, k: −9→9, l: −17→15), of which 5339 were unique. In refinements, weights were used according to the scheme $w=1/[\sigma^2(F_o)]$. The refinement converged to the final agreement factors R=0.076, and R_w=0.081, for 257 parameters and 5089 observed reflections with $F>3\sigma(F)$; data-to-parameter ratio being 19.80. The electron density of the largest difference peak was found to be 1.09 eÅ^{-3}, while that of the largest difference hole was 0.77 eÅ^{-3}.

3.2.2. Crystal data for 8. The crystal chosen for X-ray investigations was a clear colorless plate with the

approximate dimensions 0.45×0.65×0.10 mm. $C_{20}H_{24}BrNO_2$ (390.33 g mol^{-1}) crystallizes in the monoclinic system, space group $P2_1$, with a=7.8942 (5), b=11.9839 (7), c=10.3782 (8) Å, β=103.443 (5)°, V=954.9 (1) Å^3, Z=4, μ(MoKα)=2.16 mm^{-1}, and D_{calcd}=1.385 g cm^{-3}. The unit cell parameters were determined by least-squares refinement using 61 centered reflections within $10.5°<\theta<19.5°$. A total of 5293 reflections were collected in ω-scan mode to $2\theta_{max}$=55° (h: −1→10, k: −15→15, l: −13→13), of which 4354 were unique. In refinements, weights were used according to the scheme $w=1/[\sigma^2(F_o)]$. The refinement converged to the final agreement factors R=0.072, and R_w=0.063, for 217 parameters and 2983 observed reflections with $F>3\sigma(F)$; data-to-parameter ratio being 13.75. The electron density of the largest difference peak was found to be 1.54 eÅ^{-3}, while that of the largest difference hole was 0.84 eÅ^{-3}.

3.2.3. Crystal data for 14. The crystal chosen for X-ray investigations was a clear colorless prism with the approximate dimensions 0.15×0.20×0.65 mm. $C_{14}H_{16}O_3$ (232.28 g mol^{-1}) crystallizes in the monoclinic system, space group Pc, with a=8.5499 (6), b=8.5437 (5), c=8.7539 (6) Å, β=110.118 (6)°, V=600.44 (8) Å^3, Z=4, μ(MoKα)=0.09 mm^{-1}, and D_{calcd}=1.285 g cm^{-3}. The unit cell parameters were determined by least-squares refinement using 60 centered reflections within $11.2°<\theta<17.5°$. A total of 3298 reflections were collected in ω-scan mode to $2\theta_{max}$=55° (h: −11→1, k: −11→11, l: −10→11), of which 1651 were unique. In refinements, weights were used according to the scheme $w=1/[\sigma^2(F_o)]$. The refinement converged to the final agreement factors R=0.056, and R_w=0.055, for 153 parameters and 1601 observed reflections with $F>3\sigma(F)$; data-to-parameter ratio being 10.46. The electron density of the largest difference peak was found to be 0.40 eÅ^{-3}, while that of the largest difference hole was 0.36 eÅ^{-3}.

Tables of bond distances and angles, atomic coordinates, and anisotropic thermal parameters for **7** (CCDC 151691), **8** (CCDC 151690), and **14** (CCDC 151689) have been deposited with the Cambridge Crystallographic Data Centre.[37]

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