First Atropo-Divergent Total Synthesis of the Antimalarial Korupensamines A and B by the "Lactone Method"†

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The stereoselective total synthesis of the antimalarial korupensamines A (**1a**) and B (**1b**) by application of the "lactone method" is described. Key steps of this first atropo-selective access to 5,8′-coupled naphthylisoquinoline alkaloids were the regioselective intramolecular coupling of ester **8** to give the configurationally labile lactone-bridged biaryl **9** and its atropisomer-selective cleavage with a variety of chiral and achiral *H*-nucleophiles, yielding the configurationally stable *P*-diol **10a** or, optionally, the *M*-product **10b**. From the axially chiral *phenyl*isoquinolines thus obtained atropo-diastereodivergently, the authentic natural *naphthyl*isoquinolines with the respective axial configurations, korupensamines A (**1a**) and B (**1b**), were obtained by completion of the second naphthalene ring, starting from the previous "bridgehead" C_1 unit.

Introduction

The Cameroonian liana *Ancistrocladus korupensis* (Ancistrocladaceae) is a rich source of structurally, biosynthetically, and pharmacologically intriguing mono- and dimeric naphthylisoquinoline alkaloids.[1−6] Of particular interest are the 5,8′-coupled alkaloids korupensamine A (**1a**) and korupensamine B (**1b**), which exhibit good antimalarial activities in vitro[3] and in vivo.[7] Moreover, they constitute the molecular "halves" and thus both the synthetic[8] and biogenetic[9] precursors to anti-HIV[1] homo- and heterodimeric naphthylisoquinolines such as michellamine B (**2**)[2,10] and korundamine A (**3**),[5] respectively. The promising biological activities, the challenging structures, and an announcement by the US National Cancer Institute[11] triggered efforts by several research groups toward the synthetic production of naturally occurring korupensamines[12,8,13] and michellamines,[12,14,8,15−18] and synthetic structural analogues thereof.[19−25,18]

For the directed, i.e., regio- and stereoselective construction of the biaryl axis, the "lactone methodology",[26] by which numerous naphthylisoquinoline alkaloids have already been prepared highly efficiently,[26−29,20,30] seemed not to be applicable, because a fundamental structural precondition for the construction of the usual ester/lactone bridge, the presence of a C_1 substituent *ortho* to

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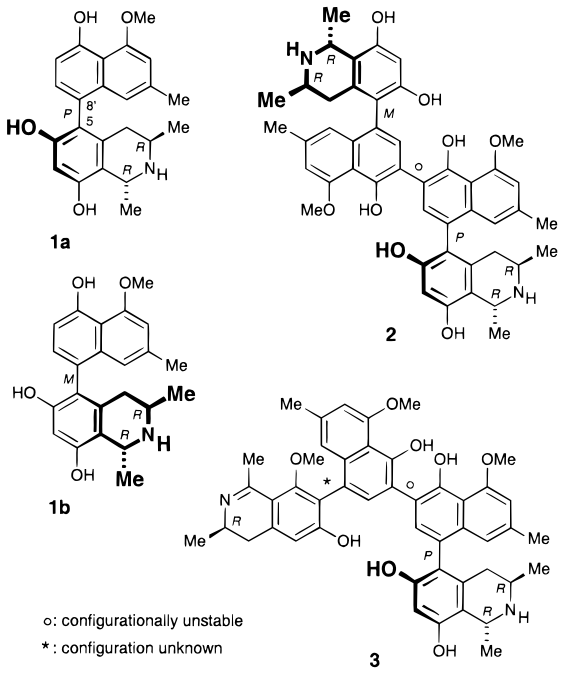
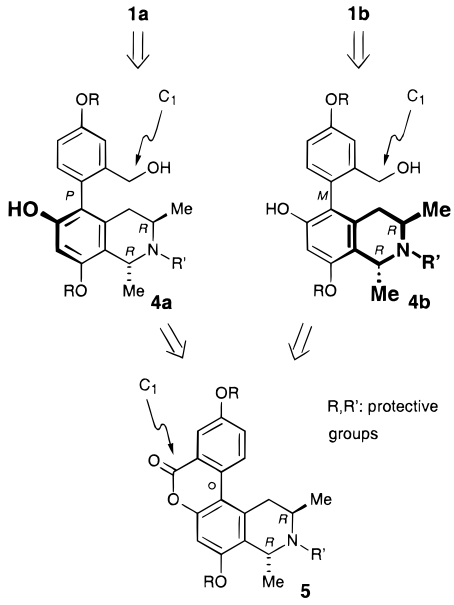


the axis, is not fulfilled for **1a** or **1b**. For this reason, our first total synthesis of **1a** and **1b** (and thus of 5,8′-coupled naphthylisoquinolines in general) succeeded by intermolecular coupling steps,[12,8] exclusively. The coupling yields, however, were moderate (ca. 21%), and the asymmetric inductions were low (1.4:1), without the possibility of a directed formation of each of the atropisomers preferentially. Subsequent korupensamine syntheses by other groups either did not give higher coupling yields or better stereoselectivities—or such syntheses did not (or not yet[31]) give the authentic natural products, but only simplified (e.g., *O*-methylated) unnatural analogues.[16,32,17,33] This led us to reconsider the lactone methodology, with all its advantages (high coupling yields and good asymmetric inductions, optional preparation of each possible atropisomer from an identical synthetically "late" precursor, the possibility of recycling undesired atropisomers by recyclization back to the lactone), for the construction of the biaryl axis of korupensamines, despite their apparent lack of a (free) C_1 unit next to the axis.[34] The resulting first atropo-divergent total synthesis of korupensamines will be described in this paper. Part of this work has previously been reported in preliminary form.[35]

Scheme 1



Results and Discussion

Our synthetic concept was based on the idea that the C_1 unit required for a realization of the lactone methodology is not really missing in korupensamines, but exists in a hidden ("cryptic") form, as part of a second naphthalene ring. With this in mind, our retrosynthetic concept (see Scheme 1) envisaged to build up korupensamines A (**1a**) and B (**1b**) from axially chiral phenyl- instead of naphthylisoquinolines (**4a** and **4b**), respectively. Their C_1 subunits next to the axis should permit a facile subsequent construction of the second naphthalene ring via a Stobbe-based approach similar to the one previously used for simple (i.e., isoquinoline-free) naphthalene systems[8] and would, at the same time, fulfill the crucial requirement for an application of the lactone methodology. These considerations suggest the biaryl lactone **5** (Scheme 1) to be a rewarding common synthetic precursor, both to **1a** and **1b**, since it meets all the requirements for a promising application of the lactone methodology—the biaryl axis in the correct position, an ester bridge as a site of attack for atropo-diasteroselective cleavage reactions, as well as *O*-isopropyl and *N*-benzyl protective groups, which have proven their suitability for naphthylisoquinoline total syntheses in numerous previous examples.[28,29,20,8,30]

Following the "lactone concept", the concrete analogue of **5**, **9**, was prepared by intramolecular biaryl coupling of the bromoester **8**, which, in turn, was synthesized from the known[36] bromo acid **6** and the likewise known[20] enantiomerically pure tetrahydroisoquinoline building block **7** (Scheme 2). Initial coupling experiments using, for example, palladium(II) acetate as the catalyst, gave quite poor yields of the lactone **9**, which is in agreement with previous experience that monocyclic aromatics may give somewhat worse coupling yields than bicyclic coupling partners.[37,38] A significant improvement resulted

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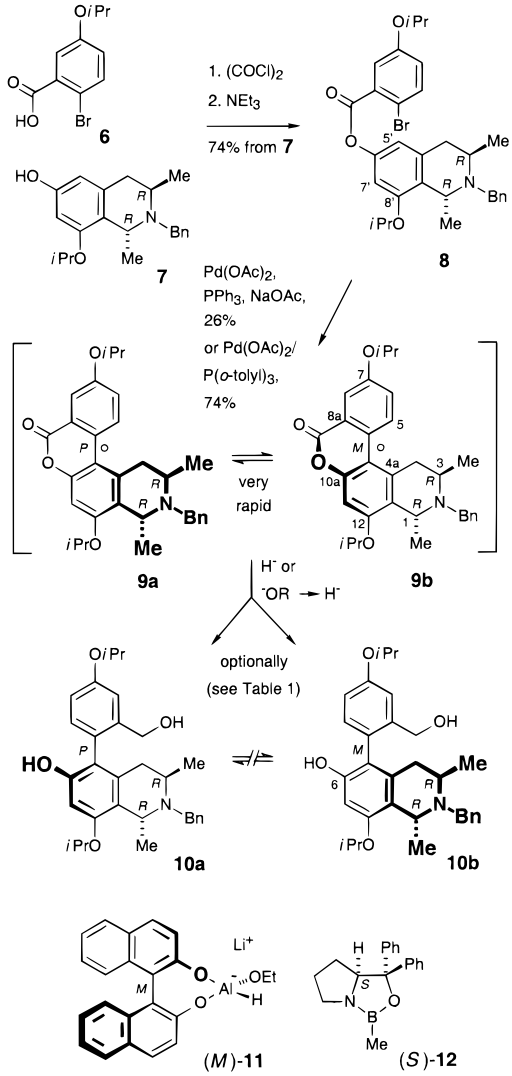
Scheme 2



from the use of the "Herrmann–Beller catalyst",[39] a binary palladium complex easily prepared from palladium(II) acetate and tris(*o*-tolyl)phosphine, now giving a far better yield of 74%. Likewise in agreement with previous naphthylisoquinoline syntheses,[40,41] the coupling occurred in the 5′-position of the isoquinoline, exclusively, while the coupling position on the benzoic acid part was predetermined by the bromine substituent. As anticipated, the lactone **9**, with the correctly positioned biaryl axis, has no stable axial chirality. Because of the rapid interconversion of its two atropo-diastereomeric forms, **9a** and **9b**, lactone **9** appears as a single species on the ^{1}H NMR time scale.

Reductive ring cleavage reactions of lactone **9** proceeded in good yields and gave quite high diastereoselectivities already with achiral hydride transfer reagents, interestingly always with the *M*-configured diol **10b**[42] as the main atropisomeric product (up to 83:17 for L-Selectride, Table 1).[43] While this would already have been a preparatively solid base for the synthesis of the likewise *M*-configured korupensamine B (**1b**), none of the achiral reagents used gave the *P*-atropisomer, preferentially. Except for η^6-metalated and thus planar-chiral biaryl lactones,[44] such high internal asymmetric induction had never been observed before for cleavage reactions with achiral *H*-nucleophiles.[45] The other approach, previously realized,[28,50] to first open the lactone by *O*-nucleophiles to the corresponding esters, and to subsequently reduce the one with the desired configuration at the axis, was hampered by the low reactivity of **9** toward *O*-nucleophiles and its high tendency to cyclize back to **9** upon attempted isolation, thus necessitating reduction (hence not resolved, again *M*-preferential) of the atropo-diastereomeric ring cleavage products in situ, using lithium aluminum hydride (LAH). No ring cleavage was observed with potassium mentholate, which had resulted in good atropisomeric excesses in other cases,[28,50] apparently due to the low degree of steric hindrance of **9** at the axis.

The high *M*-selectivity through internal asymmetric induction by the chiral environment of the lactone, in all of these cleavage reactions of **9**, was not even overcome when using the chiral hydride transfer reagent BINAL-H

Table 1. Results of the Atropo-Selective Ring Cleavage Reactions

"H$^-$"/$^-$OR	(M):(P)	yield, %
RedAl/AlMe$_3$[29]	67:33	89
RedAl	69:31	87
LAH	73:27	76
L-Selectride	83:17	83
(1) KO*i*Pr, (2) LAH	62:38	59
(1) KOMe, (2) LAH	65:35	51
K-mentholate	—[a]	—[a]
(*M*)-BINAL-H [(*M*)-**11**] (rt)	67:33	97
(*P*)-BINAL-H [(*P*)-**11**] (rt)	54:46	98
(*M*)-BINAL-H [(*M*)-**11**] (0 °C)	—[a]	—[a]
(*S*)-**12**·BH$_3$, 30 °C	87:13	58
(*S*)-**12**·BH$_3$, 0 °C	⟹ 96:4	57
(*S*)-**12**·BH$_3$, −30 °C	86:14	52
(*R*)-**12**·BH$_3$, 30 °C	13:87	69
(*R*)-**12**·BH$_3$, 0 °C	18:82	74
(*R*)-**12**·BH$_3$, −30 °C	6:94 ⟸	58

[a] No reaction.

(39) For the preparation of *trans*-di(*μ*-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) from Pd(OAc)$_2$ and 1.3 equiv of tris(*o*-tolyl)phosphine, see: Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.

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(41) Bringmann, G.; Jansen, J. R. *Heterocycles* **1989**, *28*, 137.

(42) The diols **10a** and **10b** were distinguished by NOE experiments: An interaction between 4-H$_{ax}$ and 6′-H as well as between 4-H$_{eq}$ and C*H*$_2$OH of **10b** indicated this atropo-diastereomer to be *M*-configured. This assignment was later on confirmed at the level of the final target molecules, korupensamine A (**1a**) and B (**1b**).

(43) Separation of **10a** and **10b** was performed by column chromatography.

(44) Bringmann, G.; Göbel, L.; Peters, K.; Peters, E.-M.; von Schnering, H. G. *Inorg. Chim. Acta* **1994**, *222*, 255.

(45) Quantumchemical AM1[46] calculations on **9** by the program package VAMP 6.5,[47] starting from geometries preoptimized by the TRIPOS[48] force field, indicate that a possible reason for this selectivity is the steric shielding of the upper face of the molecule by the probably axial *N*-benzyl substituent, which should adopt an antiperiplanar array to the likewise axial methyl group at C-1, which, in combination with the preferred attack of nucleophiles to the lactone functionality in an axial mode,[49] should lead to a preferred attack of nucleophiles (in particular if these are devoid of additional stereochemical information) from the bottom face, thus leading to the *M*-atropisomer.

(46) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E.; Steward, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(47) Rauhut, G.; Chandrasekhar, J.; Alex, A.; Beck, B.; Sauer, W.; Clark, T. VAMP 6.5 available from Oxford Molecular Ltd., The Medewar Centre, Oxford Science Park, Sandford-on-Thames, Oxford, OX4 4GA, England.

(48) SYBYL: Tripos Associates, 1699 St. Hanley Road, Suite 303, St. Louis, MO, 63144.

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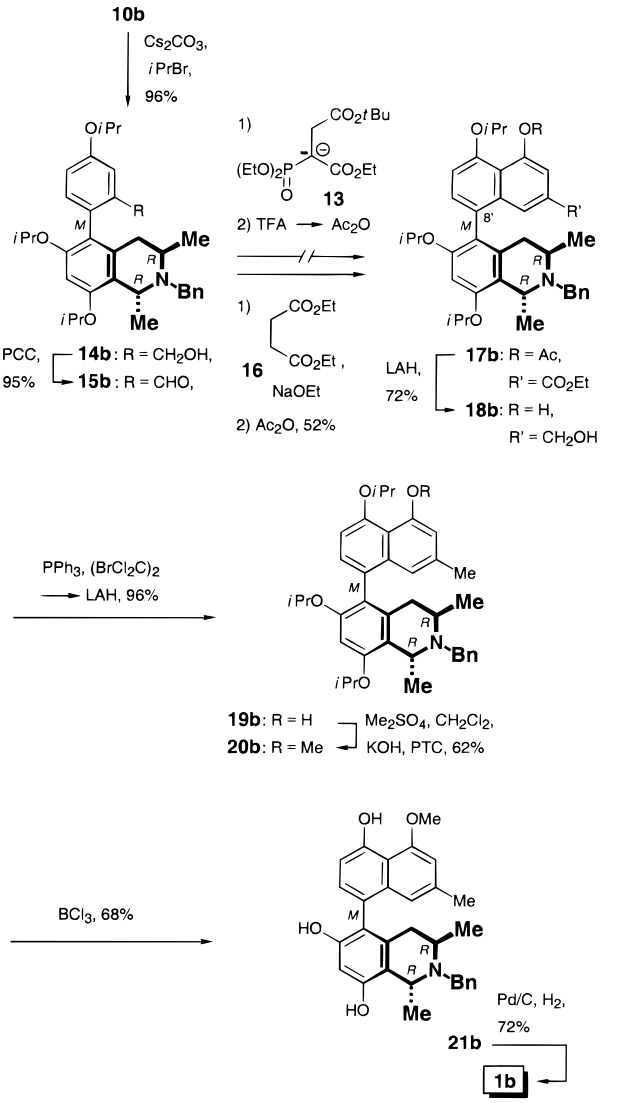
(**11**), which had led to very high external asymmetric inductions in previous experiments:[51] Again only the *M*-isomer was obtained predominantly, for both the matched and the mismatched cases: 67:33 for (*M*)-BINAL-H [(*M*)-**11**] and 54:46 for (*P*)-BINAL-H [(*P*)-**11**], see Table 1. Only by using Corey's oxazaborolidine−borane system,[52] which had given excellent external asymmetric inductions for lactones both with[30] or without[53] additional stereocenters, proved to be able to oversteer the strong molecule-inherent internal asymmetric induction, with a high diastereodivergence, giving an up to 94:6 ratio in favor of *P* for (*R*)-**12**·BH_3 and even up to 96:4 in favor of *M* for the *S*-enantiomer of the reagent.

With the biaryl axis of **10** built up optionally in its *M*- or *P*-configured form atropo-diastereodivergently, via the same lactone precursor **9**, the completion of the syntheses of korupensamines was elaborated exemplarily for korupensamine B (**1b**) first, starting with the more easily available *M*-diol **10b** (Scheme 3). Before oxidizing the CH_2OH side chain of the phenyl substituent to the aldehyde, however, the free phenolic hydroxy function at C-6 of the phenylisoquinoline **10b** had to be protected, to avoid the situation of a "stereochemical leakage" at the level of the resulting *o*-hydroxy-*o*′-formylbiaryl, since such compounds are known to be configurationally unstable, by atropo-isomerization via the corresponding hemiacetals. In order for the number of different protective groups to be kept low, the protection was again achieved by *O*-isopropylation of **10b** to give **14b**, which was further oxidized by pyridinium chlorochromate (PCC),[56] to give **15b**.

Side chain elongation of substituted benzaldehydes (like **15b**) with a succinic acid derived nucleophile and subsequent cyclization is a well-elaborated procedure for the construction of 1,8-dioxy-3-methylnaphthalenes,[57,8,58] applied in numerous syntheses, for example, of binaphthalenes[58] and naphthylisoquinoline alkaloids.[30,20] Apparently due to the increased steric shielding of the formyl group by the adjacent sterically demanding isoquinoline portion, all attempts of performing a usual[58,8] Horner−Emmons reaction with **13** as the reagent, failed completely (Scheme 3). With the ester enolate of diethyl succinate (**16**), i.e., in a Stobbe-reaction, however, the desired C,C-linkage took place quite efficiently, with subsequent ring closure by intramolecular Friedel−Crafts acylation in acetic anhydride, to give, in one pot, the required naphthalene derivative **17b**. Reduction of **17b** with LAH yielded diol **18b**. With the entire naphthylisoquinoline framework now set up, including all

Scheme 3



elements of chirality with the correct configurations, only a few further transformations had to be performed for the final target molecule, korupensamine B (**1b**), to be attained—the reductive elimination of the oxygen of the CH_2OH side chain on the naphthalene, the still required *O*-methylation at C-4′, and various deprotection reactions. Thus, hydroxy/halogen exchange by treatment with dibromotetrachloroethane/triphenylphosphine[59] and hydro-dehalogenation with LAH, followed by *O*-methylation using dimethyl sulfate with phase-transfer catalysis (PTC), yielded the still protected derivative **20b** of korupensamine B (**1b**). Its constitutional and configurational analogy to korupensamine B (**1b**) was proven at this stage of the synthesis, already, by an independent synthesis of **20b** from natural **1b** by *N*-benzylation and subsequent *O*-isopropylation (not shown, see Experimental Section).

Deprotection of **20b** was finally achieved by simultaneous cleavage of the three isopropyl ethers with boron trichloride[60,61] to give **21b**, and *N*-debenzylation of the amino function by palladium-catalyzed hydrogenation, to

(51) Bringmann, G.; Breuning, M. *Tetrahedron*: *Asymmetry* **1999**, *10*, 385.

(52) For a review on the oxazaborolidine-borane reagent, mainly for the reduction of carbonyl compounds, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(53) For previous, atropo-*enantioselective* biaryl lactone cleavage reactions using the oxazaborolidine−BH_3 system, see refs 54, 38, and 55.

(54) Bringmann, G.; Hartung, T. *Tetrahedron* **1993**, *49*, 7891.

(55) Bringmann, G.; Breuning, M. *Tetrahedron: Asymmetry* **1998**, *9*, 667.

(56) The use of manganese dioxide did not lead to a quantitative conversion of **14b** to **15b**.

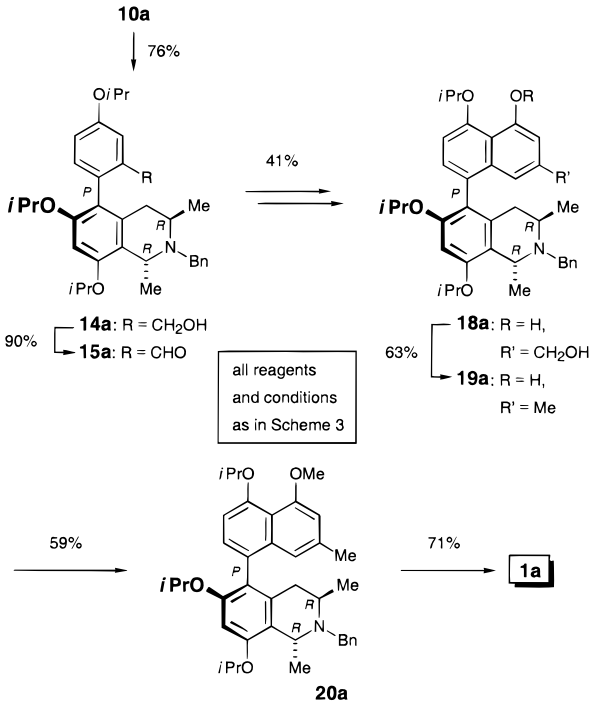
(57) For an easier comparison of the isoquinoline-free naphthalene with the naphthyl parts of the corresponding alkaloids even of different coupling types, a 2-methyl-4,5-dioxy substitution pattern is applied throughout in the numbering of these naphthalenes, regardless of the presence of a biaryl axis; see also ref 27.

(58) Bringmann, G.; Ortmann, T.; Feineis, D.; Peters, E.-M.; Peters, K. *Synthesis*, in press.

(59) Bringmann, G.; Schneider, S. *Synthesis* **1983**, 139.

(60) (a) Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2593. (b) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981.

Scheme 4



give **1b** (Scheme 3), which proved to be identical in all its chromatographic, physical, and spectral data with material isolated from *A. korupensis*[3] and to material from previous syntheses.[8]

With the reaction sequence optimized for the *M*-atropisomeric series, to give korupensamine B (**1b**), the corresponding synthesis of korupensamine A (**1a**) from **10a** was carried out in a fully analogous way (Scheme 4), key intermediates being the primary alcohol **14a**, the aldehyde **15a**, the diol **18a**, the methyl compound **19a**, and the fully protected analogue **20a** of korupensamine A (**1a**). Again, the target molecule **1a** ultimately obtained, was fully identical to a genuine sample of korupensamine A from *A. korupensis*[3] and to synthetic material from previous work.[8]

Conclusions

The work presented in this paper constitutes the first directed, i.e., atropo-divergent total synthesis of korupensamines A (**1a**) and B (**1b**), via a joint, configurationally unstable lactone precursor **10**. Besides the importance of the work for the preparation of antimalarial korupensamines and their anti-HIV dimers, the michellamines, the work demonstrates the flexibility of the lactone methodology, here in the synthesis of an axially chiral target biaryl without a free C_1 unit next to the biaryl axis. Together with other already realized or still potential possibilities of subsequently transforming the oxygen[34] and C_1 substituents required for the lactone formation, into other functional groups (i.a., into phosphine ligands[62]), the results show that a broad spectrum of axially chiral target molecules with virtually any substitution pattern can in principle be attained, together with the other advantages of the lactone methodology.[26] Further total syntheses of axially chiral biaryl natural products, including nonalkaloidal target molecules by application of the concept, are in progress.

Experimental Section

General. HPLC−UV: Waters HPLC Pump 510, Rheodyne 7125 Syringe Loading sample injector, Shimadzu C−R6-A integrator. Column: Chiracel OD-H (250 × 4.25 mm, 1 mL/min), *n*-hexane/*i*-PrOH (95:5): t_R = 13.5 min for **10a**, t_R = 20.8 min for **10b**. MPLC−UV: Latek Pump P400. Column: Lobar RP-18 (size B, Merck). Source of compounds: **6**,[36] **7**,[20] and **11**[51] were prepared according to literature procedures. For further general procedures (i.a., $[\alpha]_D$, mp, NMR, IR, MS, chromatography), see refs 30 and 8.

(1′*R*,3′*R*)-*N*-Benzyl-8′-isopropoxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydroisoquinolin-6′-yl 2-Bromo-5-isopropoxy-1-benzoate (8). To a suspension of **6**[36] (293 mg, 1.13 mmol) in 13 mL of dry CH_2Cl_2 were added dropwise a catalytic amount of dry DMF (10 μL) and oxalyl chloride (103 μL, 1.31 mmol) under nitrogen at 0 °C, and the reaction mixture was stirred for 4 h at this temperature. After slow addition of a solution of **7**[20] (283 mg, 871 μmol) and NEt_3 (361 μL, 2.61 mmol) in 13 mL of dry CH_2Cl_2 and stirring for another 5 h, the solvent was removed in vacuo and the residue was chromatographed on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 100:0.5) to give 362 mg (74%) of **8** as an amorphous slightly yellow solid: $[\alpha]^{25}_D$ = +48.4 (*c* 0.33, $CHCl_3$); IR (KBr) ν 2960, 2920, 1740, 1580, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60 (3H, d, *J* = 6.2 Hz), 1.27 (3H, d, *J* = 6.1 Hz), 1.28 (3H, d, *J* = 5.9 Hz), 1.31 (3H, d, *J* = 6.6 Hz), 1.36 (6H, d, *J* = 6.2 Hz), 2.57−2.70 (2H, m), 3.27 (1H, d, *J* = 14.0 Hz), 3.52 (1H, m_c), 3.83 (1H, d, *J* = 14.0 Hz), 3.93 (1H, q, *J* = 7.0 Hz), 4.47 (1H, sept, *J* = 6.2 Hz), 4.57 (1H, sept, *J* = 5.9 Hz), 6.55 (1H, br), 6.58 (1H, br), 6.93 (1H, dd, *J* = 8.8 Hz, *J* = 3.0 Hz), 7.23−7.37 (5H, m), 7.50 (1H, d, *J* = 2.9 Hz), 7.58 (1H, d, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.19, 20.43, 22.49, 22.58, 22.64, 32.86, 46.26, 50.54, 52.18, 70.61, 71.34, 104.30, 112.73, 113.58, 119.55, 121.61, 127.01, 127.37, 128.65, 129.19, 132.83, 135.96, 137.74, 141.87, 149.80, 156.82, 157.63; MS (EI) *m*/*z* 567/565 (0.2/0.7) [M^+], 552/550 (68/72) [$M^+ - CH_3$], 510/508 (12/12), 243/241 (18/20), 201/199 (23/23), 91 (100). Anal. Calcd for $C_{31}H_{36}BrNO_4$ (HCl salt): C, 61.75; H, 6.18; N, 2.32. Found: C, 61.47; H, 6.10; N, 2.25.

Lactone 9. (A) Using $Pd(OAc)_2$ as the Catalyst. After heating a mixture of **8** (150 mg, 265 μmol), $Pd(OAc)_2$ (5.95 mg, 26.5 μmol), PPh_3 (13.9 mg, 52.9 μmol), and NaOAc (43.4 mg, 529 μmol) for 6 h at 60 °C in vacuo, 5 mL of dry *N*,*N*-dimethylacetamide (DMA) was added, and the solution was stirred for 18 h at 120 °C under nitrogen. The solvent was removed under reduced pressure, CH_2Cl_2/MeOH (99:1) was added, and the mixture was filtered over Celite. Removal of the solvent in vacuo and column chromatography on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 99:1) afforded **9** (33.0 mg, 26%) as an amorphous, slightly yellow solid, fluorescent in solution at 366 nm.

(B) Using the ′Herrmann−Beller Palladium Catalyst′.[39] To a solution of ester **8** (362 mg, 639 μmol) in 6 mL of dry DMA, NaOAc (105 mg, 1.28 mmol) and the binary palladium complex[39] (63.8 mg, 63.9 μmol), prepared from $Pd(OAc)_2$ and tris(*o*-tolyl)phosphine as the catalyst, in 4 mL of dry DMA were added at 80 °C. After stirring the reaction mixture at 140 °C for 22 h, the solvent was evaporated under reduced pressure, CH_2Cl_2/MeOH (99:1) was added, and the mixture was filtered over Celite. Removal of the solvent in vacuo and column chromatography on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 99:1) gave **9** (230 mg, 74%), identical to the material obtained above.

$[\alpha]^{24}_D$ = +159.4 (*c* 0.27, $CHCl_3$); IR (KBr) ν 2940, 2900, 1710, 1580; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.28 (6H, *J* = 6.1 Hz, OCH_3CHCH_3, CH_3 at C-3, overlapping), 1.35 (3H, d, *J* = 6.0 Hz, OCH_3CHCH_3), 1.38 (3H, d, *J* = 6.4 Hz, CH_3 at C-1), 1.40 (3H, d, *J* = 6.0 Hz, OCH_3CHCH_3), 1.41 (3H, d, *J* = 6.1 Hz, OCH_3-

(61) For previous examples of selective *O*-deisopropylation reactions in the presence of methoxy groups[60] in the field of naphthylisoquinoline alkaloids, see refs 27, 12, 8, and 20.

(62) Bringmann, G.; Wuzik, A.; Breuning, M.; Henschel, P.; Peters, K.; Peters, E.-V. *Tetrahedron: Asymmetry* **1999**, *10*, 3025.

$CHCH_3$), 3.04 (1H, dd, J = 15.9 Hz, J = 9.4 Hz, 4-H_{ax}), 3.16 (1H, dd, J = 15.9 Hz, J = 4.2 Hz, 4-H_{eq}), 3.48 (1H, m_c, 3-H), 3.52 (1H, d, J = 13.9 Hz, NC*H*HPh), 3.86 (1H, d, J = 13.9 Hz, NCH*H*Ph), 4.06 (1H, q, J = 6.5 Hz, 1-H), 4.58 [1H, sept, J = 6.0 Hz, O*CH*$(CH_3)_2$], 4.73 [1H, sept, J = 6.0 Hz, O*CH*$(CH_3)_2$], 6.78 (1H, s, 11-H), 7.24−7.26 (1H, m, 4′-H), 7.31−7.34 (3H, m, 6-H, 3′-H, 5′-H, overlapping), 7.39 (2H, d, J = 7.3 Hz, 2′-H, 6′-H), 7.90 (1H, d, J = 3.0 Hz, 8-H), 8.27 (1H, d, J = 9.2 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.01 (CH_3 at C-3), 20.24 (CH_3 at C-1), 21.73 [$CH(CH_3)_2$], 21.92 [$CH(CH_3)_2$], 35.93 (C-4), 46.09 (C-3), 50.88 (NCH_2Ph), 51.68 (C-1), 70.24 [O*C*H$(CH_3)_2$ at C-12 or C-7], 70.37 [O*C*H$(CH_3)_2$ at C-12 or C-7], 99.45 (C-11), 109.70 (C-4b), 113.81 (C-8), 122.46 (C-8a), 124.18, 126.62, 127.60 (C-5), 128.12, 128.58, 129.60 (C-4c), 133.49 (C-4a), 140.63, 150.58 (C-10a), 155.39 (C-12), 156.42 (C-7), 161.80 (C=O). The ^{1}H and ^{13}C attributions were achieved by Heteronuclear Multiple Quantum Correlation (HMQC), Heteronuclear Multiple Bond Correlation (HMBC), and DEPT experiments. MS (EI) m/z 485 (0.4) [M^+], 470 (53) [$M^+ - CH_3$], 428 (15), 386 (4), 91 (100). Anal. Calcd for $C_{31}H_{35}NO_4$: C, 76.67; H, 7.26; N, 2.88. Found: C, 76.61; H, 7.20; N, 2.88.

Atroposelective Ring Cleavage of 9 (Preparative Scale). To **9** (50.8 mg, 105 μmol) in 5 mL of dry THF was added a solution of (*P*)-**11**[51] (4.18 μmol) in dry THF (3.73 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for 4 h. Hydrolysis with H_2O (100 μL), removal of the solvent in vacuo, and filtration of the residue on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 9:1) gave a crude product, which was purified by column chromatography on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 9:1) to yield the diastereomers **10a** (22.4 mg, 44%) and **10b** (25.3 mg, 49%) as amorphous solids in a 53:47 ratio.

(1*R*,3*R*,5*P*)-*N*-Benzyl-6-hydroxy-5-(2′-hydroxymethyl-4′-isopropoxy-1′-phenyl)-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (10a): 22.4 mg (44%); $[\alpha]^{25}_D$ = +91.8 (*c* 0.33, $CHCl_3$); IR (KBr) ν 3600−3100, 2980, 1600, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 (3H, d, J = 6.7 Hz), 1.25 (3H, d, J = 6.0 Hz), 1.30 (3H, d, J = 5.8 Hz), 1.33 (3H, d, J = 6.5 Hz), 1.40 (6H, d, J = 6.0 Hz), 1.92 (1H, dd, J = 17.6 Hz, J = 11.0 Hz), 2.19 (1H, dd, J = 17.5 Hz, J = 4.6 Hz), 3.22 (1H, d, J = 14.0 Hz), 3.40 (1H, m_c), 3.73 (1H, d, J = 13.9 Hz), 3.95 (1H, q, J = 6.6 Hz), 4.34 (2H, s), 4.48 (1H, sept, J = 6.2 Hz), 4.64 (1H, sept, J = 6.1 Hz), 6.41 (1H, s), 6.93 (1H, dd, J = 8.4 Hz, J = 2.6 Hz), 7.10 (1H, d, J = 8.4 Hz), 7.14 (1H, d, J = 2.5 Hz), 7.21−7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.37, 20.05, 21.98, 22.16, 30.86, 45.73, 50.04, 51.47, 63.58, 69.60, 97.81, 115.69, 116.05, 116.76, 121.02, 124.87, 126.39, 128.00, 128.63, 132.74, 135.20, 141.13, 142.28, 151.69, 156.12, 158.36; MS (EI) m/z 489 (0.3) [M^+], 474 (100) [$M^+ - CH_3$], 456 (3), 432 (2), 414 (5), 91 (20); HRMS calcd for $C_{30}H_{36}NO_4$ 474.2644, found: 474.2652.

(1*R*,3*R*,5*M*)-*N*-Benzyl-6-hydroxy-5-(2′-hydroxymethyl-4′-isopropoxy-1′-phenyl)-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (10b). An analytical amount of **10b** was obtained by recrystallization from CH_2Cl_2/petroleum ether as colorless needles, mp 85 °C: $[\alpha]^{25}_D$ = +91.8 (*c* 0.33, $CHCl_3$); IR (KBr) ν 3600−3100, 2980, 1600, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (3H, d, J = 6.7 Hz), 1.25 (3H, d, J = 6.0 Hz), 1.30 (3H, d, J = 5.8 Hz), 1.33 (3H, d, J = 6.5 Hz), 1.40 (6H, d, J = 6.0 Hz), 1.92 (1H, dd, J = 17.6 Hz, J = 11.0 Hz), 2.19 (1H, dd, J = 17.5 Hz, J = 4.6 Hz), 3.22 (1H, d, J = 14.0 Hz), 3.40 (1H, m_c), 3.73 (1H, d, J = 13.9 Hz), 3.95 (1H, q, J = 6.6 Hz), 4.34 (2H, s), 4.48 (1H, sept, J = 6.2 Hz), 4.64 (1H, sept, J = 6.1 Hz), 6.41 (1H, s), 6.93 (1H, dd, J = 8.4 Hz, J = 2.6 Hz), 7.10 (1H, d, J = 8.4 Hz), 7.14 (1H, d, J = 2.5 Hz), 7.21−7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.64, 20.03, 22.13, 22.19, 22.22, 31.45, 45.94, 50.18, 51.61, 63.71, 69.81, 70.04, 98.26, 115.82, 116.14, 116.91, 121.61, 125.18, 126.34, 127.98, 128.59, 132.85, 135.14, 141.43, 141.86, 151.72, 156.16, 158.48; MS (EI) m/z 474 (39) [$M^+ - CH_3$], 456 (7), 414 (9), 91 (100); HRMS calcd for $C_{30}H_{36}NO_4$ 474.2644, found: 474.2641. Anal. Calcd for $C_{31}H_{39}NO_4 \cdot CH_2Cl_2$ (content of CH_2Cl_2 confirmed by ^{1}H NMR on freshly dissolved crystals): C, 71.29; H, 7.66; N, 2.60. Found: C, 71.18; H, 7.70; N, 2.66.

General Procedure for the Reduction of 9 with Lithium Tri-*sec*-butylborohydride (L-Selectride) or Sodium Bis(2-methoxyethoxy)aluminum Hydride (Red-Al) (Analytical Scale). Ester **9** (10.0 mg, 20.6 μmol) was dissolved in 2 mL of dry THF, 5 equiv of a solution of the reducing agent (as purchased from Aldrich) was added at −70 °C under argon, and the suspension was stirred for 2 h. After quenching the reaction mixture with 2 N HCl, the solvent was removed in vacuo, and the residue was purified by preparative TLC on deactivated (atmosphere saturated with aqueous NH_3) silica gel (CH_2Cl_2/MeOH = 95:5).

Reduction of 9 with Sodium Bis(2-methoxyethoxy)-aluminum Hydride (Red-Al) and $AlMe_3$ (Analytical Scale). To **9** (7.50 mg, 15.4 μmol) in 1 mL of dry THF were added $AlMe_3$ (9.26 mg, 18.5 μmol) and 20.0 μL of RedAl (1.0 M solution in dry THF) under argon at −70 °C. The suspension was stirred for 20 min and quenched with H_2O. The products were purified on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 98:2 → 96:4).

Reduction of 9 with Oxazaborolidine-Activated Borane (Analytical Scale). After dissolving **9** (10.0 mg, 20.6 μmol) in 0.5 mL of dry THF under argon, a solution of 94.7 μmol of oxazaborolidine (**12**, 1.0 M solution in toluene) and 126 μmol of BH_3 (1.0 M solution in THF) were added. The suspension was stirred for 2 h. Workup as described above.

Conversion of 9 with KO*i*Pr or NaOMe and Reduction with LAH (Analytical Scale). A solution of **9** (2.00 mg, 4.11 μmol) in 0.5 mL of dry THF was treated with 20 μL of a solution of the respective alkali metal (0.398 M in dry *i*-PrOH or MeOH) and stirred for 2 h at room temperature under argon. After addition of 600 μL of LAH (1.0 M solution in THF), the mixture was stirred for 30 min, and 1 mL of petroleum ether was added. Workup as described above.

(1*R*,3*R*,5*M*)-*N*-Benzyl-5-(2′-hydroxymethyl-4′-isopropoxy-1′-phenyl)-6,8-diisopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (14b). A mixture of **10b** (212 mg, 433 mmol), Cs_2CO_3 (174 mg, 535 μmol), and *i*-PrBr (126 μL, 1.34 mmol) in 6 mL of acetone was stirred for 16 h at 40 °C. After further addition of *i*-PrBr (105 μL, 1.11 mmol) and stirring for 24 h at 40 °C, the solvent was removed in vacuo and the residue was purified by chromatography on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 100:2 → 100:8) to yield **14b** as an amorphous, slightly yellow solid (220 mg, 96%): $[\alpha]^{25}_D$ +134.1 (*c* 0.30, $CHCl_3$); IR (KBr) ν 3600-3100, 2940, 2920, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92 (3H, d, J = 6.1 Hz), 1.12 (3H, d, J = 6.6 Hz), 1.19 (3H, d, J = 6.1 Hz), 1.23 (3H, d, J = 6.1 Hz), 1.31 (3H, d, J = 6.8 Hz), 1.32 (3H, d, J = 6.0 Hz), 1.39 (6H, d, J = 6.1 Hz), 1.85 (1H, dd, J = 17.6 Hz, J = 4.4 Hz), 2.27 (1H, dd, J = 17.6 Hz, J = 11.6 Hz), 3.10 (1H, br), 3.32 (1H, d, J = 14.1 Hz), 3.33 (1H, m_c), 3.79 (1H, d, J = 14.1 Hz), 3.97 (1H, q, J = 6.7 Hz), 4.12 (1H, sept, J = 6.1 Hz), 4.23 (2H, br), 4.48 (1H, sept, J = 6.1 Hz), 4.64 (1H, sept, J = 6.1 Hz), 6.42 (1H, s), 6.87 (1H, dd, J = 8.4 Hz, J = 2.6 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.07 (1H, d, J = 2.6 Hz), 7.19−7.41 (5H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.82, 19.93, 22.02, 22.17, 31.57, 45.87, 49.90, 51.71, 64.67, 69.63, 69.84, 73.60, 101.15, 115.46, 116.44, 123.34, 126.33, 128.00, 128.56, 131.83, 133.41, 135.79, 140.76, 141.40, 153.57, 155.24, 157.20; MS (EI) m/z 531 (0.4) [M^+], 516 (71) [$M^+ - CH_3$], 474 (9), 414 (9), 91 (100); HRMS calcd for $C_{33}H_{42}NO_4$ 516.3114, found: 516.3111. Anal. Calcd for $C_{34}H_{45}NO_4 \cdot H_2O$ (content of H_2O confirmed by ^{1}H NMR on freshly dissolved material): C, 74.28; H, 8.62; N, 2.55. Found: C, 74.61; H, 8.61; N, 2.48.

(1*R*,3*R*,5*M*)-*N*-Benzyl-5-(2′-formyl-4′-isopropoxy-1′-phenyl)-6,8-diisopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (15b). To a solution of **14b** (144 mg, 271 μmol) in 10 mL of dry THF were added 204 mg (947 μmol) of PCC in portions over a period of 8 h at room temperature under argon. The reaction mixture was adjusted to pH 7 with a saturated aqueous $NaHCO_3$ solution, and the solvent was evaporated in vacuo. Purification was achieved by column chromatography using deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 98:2) to yield **15b** as an amorphous, slightly yellow solid (136 mg, 95%): $[\alpha]^{23}_D$ = +107.9 (*c* 0.37, $CHCl_3$); IR (KBr) ν 2940, 2900, 1670, 1580, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.05 (3H,

d, J = 6.1 Hz), 1.10 (3H, d, J = 6.1 Hz), 1.12 (3H, d, J = 6.6 Hz), 1.23 (3H, d, J = 5.9 Hz), 1.31 (3H, d, J = 6.1 Hz), 1.32 (3H, d, J = 5.9 Hz), 1.40 (6H, d, J = 6.0 Hz), 1.99 (1H, dd, J = 17.4 Hz, J = 4.3 Hz), 2.30 (1H, dd, J = 17.3 Hz, J = 11.6 Hz), 3.33 (1H, d, J = 14.0 Hz), 3.35 (1H, m_c), 3.79 (1H, d, J = 13.9 Hz), 3.96 (1H, q, J = 6.7 Hz), 4.23 (1H, sept, J = 6.0 Hz), 4.50 (1H, sept, J = 6.0 Hz), 4.69 (1H, sept, J = 6.1 Hz), 6.37 (1H, s), 7.14 (1H, d, J = 8.3 Hz), 7.16 (1H, dd, J = 8.7 Hz, J = 2.7 Hz), 7.23 (1H, dd, J = 7.3 Hz, J = 7.3 Hz), 7.30 (2H, dd, J = 7.6 Hz, J = 7.5 Hz), 7.36 (2H, d, J = 7.5 Hz), 7.49 (1H, d, J = 2.6 Hz), 9.67 (1H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.67, 19.89, 22.04, 22.10, 31.80, 45.84, 50.03, 51.54, 69.83, 70.10, 70.98, 98.36, 110.97, 118.46, 121.98, 122.86, 126.37, 128.00, 128.56, 133.11, 134.41, 135.23, 135.80, 141.29, 154.18, 155.85, 157.06, 193.26; MS (EI) m/z 529 (0.1) [M^+], 514 (55) [$M^+ - CH_3$], 472 (11), 430 (11), 91 (100); HRMS calcd for $C_{33}H_{40}NO_4$ 514.2957, found: 514.2957.

(1*R*,3*R*,5*M*)-*N*-Benzyl-5-(4′-acetoxy-2′-carboxyethyl-5′-isopropoxy-8′-naphthyl)-6,8-diisopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (17b). To a solution of **15b** (124 mg, 288 μmol) in 2 mL of dry EtOH were added 3 mL of a 0.435 M solution of sodium in dry EtOH and diethyl succinate (**16**, 71.9 μL, 432 μmol) under argon and stirred for 2 h at 60 °C. After addition of a further amount of **16** (50.0 μL, 301 μmol), the solution was stirred for additional 6.5 h at 50 °C. The solvent was evaporated, and the residue was dried for several hours in vacuo. The residue was dissolved in 15 mL of acetic acid anhydride and stirred for 10.5 h at 120 °C under nitrogen. The reaction mixture was quenched with H_2O (200 μL), the solvent was removed in vacuo, and the residue was suspended in water and extracted with CH_2Cl_2. After evaporation of the solvent of the organic layers in vacuo, the residue was dissolved in MeOH and the solution was adjusted to pH 10 with concd aqueous NH_3. The solvent was removed in vacuo, and the residue was filtered on basic alumina (6% H_2O) using CH_2Cl_2/MeOH = 10:1. Column chromatography on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 100:0.5 → 100:1) afforded **17b** as an amorphous crude product (102 mg, 52%), fluorescent in solution at 366 nm, which was used in the next reaction without further purification. An analytical sample of **17b** was obtained by preparative HPLC (RP-18 Waters Nova Pak, 3.9 × 150 mm) with MeOH/H_2O/TFA = 70:30:0.001 as the eluent: $[\alpha]^{25}_D$ = +51.8 (c 0.39, $CHCl_3$); IR (KBr) ν 2940, 2900, 1700, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (3H, d, J = 6.1 Hz), 0.97 (3H, d, J = 6.1 Hz), 1.05 (3H, d, J = 6.7 Hz), 1.25 (3H, t, J = 5.8 Hz), 1.32−1.37 (9H, m), 1.47 (6H, d, J = 6.1 Hz), 1.83 (1H, dd, J = 26.1 Hz, J = 4.9 Hz), 2.16 (1H, dd, J = 28.8 Hz, J = 17.2 Hz), 2.42 (3H, s), 3.32 (1H, d, J = 13.8 Hz), 3.32 (1H, m_c), 3.77 (1H, d, J = 14.3 Hz), 4.00 (1H, q, J = 7.0 Hz), 4.19 (1H, sept, J = 6.0 Hz), 4.31 (2H, q, J = 7.0 Hz), 4.53 (1H, sept, J = 6.1 Hz), 4.79 [sept, J = 6.2 Hz, 1 H, OC*H*$(CH_3)_2$], 6.45 (s, 1 H, 7-H), 7.03 (1H, d, J = 8.5 Hz), 7.22−7.39 (6H, m), 7.58 (1H, d, J = 1.7 Hz), 8.09 (1H, d, J = 1.7 Hz); MS (EI) m/z 666 (11) [$M^+ - CH_3$], 644 (9), 91 (100); HRMS calcd for $C_{41}H_{48}NO_7$ 666.3431, found: 666.3421.

Analogous treatment of **15b** with **13**,[63] according to a procedure described in ref 7, did not show any detectable reaction.

(1*R*,3*R*,5*M*)-*N*-Benzyl-5-(4′-hydroxy-2′-hydroxymethyl-5′-isopropoxy-8′-naphthyl)-6,8-diisopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (18b). A solution of **17b** (40.5 mg, 59.4 μmol) in 1 mL of dry THF was treated with 119 μL of a 1.0 M solution of LAH in dry THF and stirred for 2 h at 0 °C. After removal of the solvent in vacuo, the residue was suspended in H_2O and neutralized with 2 N HCl. Extraction with CH_2Cl_2, evaporation of the solvent of the organic layers in vacuo, and chromatography on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 100:0.6 → 9:1) gave **18b** as an amorphous solid (25.5 mg, 72%): $[\alpha]^{24}_D$ = +43.7 (c 0.41, $CHCl_3$); IR (KBr) ν 3600-3100, 2950, 2910, 1620, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (3H, d, J = 6.1 Hz), 0.98 (3H, d, J = 6.1 Hz), 1.04 (3H, d, J = 6.6 Hz), 1.24 (3H, d, J = 6.0 Hz), 1.36 (3H, d, J = 7.2 Hz), 1.38 (3H, d, J = 6.1 Hz), 1.55 (3H, d, J = 6.0 Hz), 1.56 (3H, d, J = 6.1 Hz), 1.86 (1H, dd, J = 17.5 Hz, J = 4.6 Hz), 2.19 (1H, dd, J = 17.7 Hz, J = 11.3 Hz), 3.31 (1H, d, J = 13.9 Hz), 3.31 (1H, m_c), 3.75 (1H, d, J = 13.7 Hz), 3.99 (1H, q, J = 6.6 Hz), 4.13 (1H, sept, J = 6.0 Hz), 4.52 (1H, sept, J = 5.9 Hz), 4.63 (2H, br), 4.91 (1H, sept, J = 5.9 Hz), 6.45 (1H, s), 6.87 (1H, d, J = 8.1 Hz), 6.87 (1H, s), 6.87 (1H, s), 7.12 (1H, d, J = 8.0 Hz), 7.21−7.39 (6H, m), 9.95 (1H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.67, 20.05, 22.13, 22.21, 22.33, 30.94, 45.89, 49.98, 51.59, 65.63, 69.78, 71.63, 72.77, 99.65, 106.42, 108.74, 114.88, 115.53, 121.92, 122.04, 126.31, 127.97, 128.16, 128.63, 129.73, 136.05, 136.17, 139.91, 141.40, 153.16, 154.68, 155.30, 155.39; MS (EI) m/z 582 (11) [$M^+ - CH_3$], 516 (11), 91 (100); HRMS calcd for $C_{37}H_{44}NO_5$ 582.3219, found: 582.3223.

(1*R*,3*R*,5*M*)-*N*-Benzyl-5-(4′-hydroxy-5′-isopropoxy-2′-methyl-8′-naphthyl)-6,8-diisopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (19b). A mixture of **18b** (8.16 mg, 13.7 μmol) in 1 mL of dry CH_2Cl_2, PPh_3 (5.28 mg, 20.1 μmol), and $(BrCl_2C)_2$ (8.00 mg, 24.5 μmol) was stirred under argon for 3 h at room temperature. The solvent was evaporated, the residue was dissolved in 1 mL of dry THF, and 5 equiv of LAH (1.0 M solution in THF) were added at 0 °C. After stirring for 30 min at 0 °C and addition of diethyl ether (1 mL) and H_2O (100 μL), the solvent was evaporated and the residue was purified by chromatography on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 100:0.2) to yield **19b** as an amorphous solid (7.60 mg, 96%): $[\alpha]^{25}_D$ = +66.9 (c 0.38, $CHCl_3$); IR (KBr) ν 2940, 1580, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.90 (3H, d, J = 6.1 Hz), 0.99 (3H, d, J = 6.0 Hz), 1.04 (3H, d, J = 6.5 Hz), 1.23 (3H, d, J = 6.0 Hz), 1.35 (3H, d, J = 6.1 Hz), 1.37 (3H, d, J = 7.1 Hz), 1.54 (3H, d, J = 5.7 Hz), 1.55 (3H, d, J = 5.7 Hz), 1.91 (1H, dd, J = 17.9 Hz, J = 4.1 Hz), 2.18 (1H, dd, J = 17.5 Hz, J = 11.5 Hz), 2.29 (3H, s), 3.31 (1H, d, J = 14.0 Hz), 3.32 (1H, m_c), 3.76 (1H, d, J = 13.7 Hz), 3.99 (1H, q, J = 6.7 Hz), 4.12 (1H, sept, J = 6.0 Hz), 4.52 (1H, sept, J = 5.9 Hz), 4.89 (1H, sept, J = 6.0 Hz), 6.46 (1H, s), 6.66 (1H, s), 6.68 (1H, s), 6.80 (1H, d, J = 8.0 Hz), 7.07 (1H, d, J = 7.9 Hz), 7.22 (1H, dd, J = 7.3 Hz, J = 7.3 Hz), 7.29 (2H, dd, J = 7.6 Hz, J = 7.6 Hz), 7.36 (2H, d, J = 7.2 Hz), 9.85 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.70, 20.08, 21.87, 21.99, 22.10, 22.15, 22.23, 22.34, 30.85, 45.92, 50.01, 51.84, 69.83, 71.72, 72.61, 99.95, 105.51, 111.71, 114.25, 116.52, 121.96, 122.59, 126.30, 127.77, 127.95, 128.64, 128.74, 129.73, 136.18, 136.26, 137.08, 141.45, 153.19, 154.56, 154.77, 155.26; MS (EI) m/z 581 (0.4) [M^+], 566 (8) [$M^+ - CH_3$], 500 (19), 91 (100); HRMS calcd for $C_{37}H_{44}NO_4$ 566.3270, found: 566.3274.

(1*R*,3*R*,5*M*)-*N*-Benzyl-5-(5′-isopropoxy-4′-methoxy-2′-methyl-8′-naphthyl)-6,8-diisopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (20b). (A) From 19b. A reaction mixture of **19b** (3.82 mg, 6.58 μmol), Me_2SO_4 (10.0 μL), 1 mL of a 1.0 M aqueous KOH solution in H_2O, benzyltri-*n*-butylammonium chloride (1 mg), and 1 mL of CH_2Cl_2 were stirred for 1 h at room temperature with ultrasonic treatment. Purification of **20b** was performed by adding a small amount of concd aqueous NH_3, extraction with CH_2Cl_2, evaporation of the solvent of the organic layers in vacuo, and chromatography on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 100:1) to yield **20b** as an amorphous solid (2.43 mg, 62%). $[\alpha]^{25}_D$ = +36.4 (c 0.31, $CHCl_3$); IR (KBr) ν 2940, 2900, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (3H, d, J = 6.1 Hz), 0.93 (3H, d, J = 6.1 Hz), 1.03 (3H, d, J = 6.6 Hz), 1.23 (3H, d, J = 6.0 Hz), 1.35 (3H, d, J = 6.0 Hz), 1.37 (3H, d, J = 6.7 Hz), 1.43 (6H, d, J = 6.0 Hz), 1.88 (1H, dd, J = 17.7 Hz, J = 5.0 Hz), 2.19 (1H, dd, J = 17.7 Hz, J = 11.3 Hz), 2.33 (3H, s), 3.30 (1H, d, J = 14.0 Hz), 3.31 (1H, m_c), 3.76 (1H, d, J = 14.2 Hz), 3.96 (3H, s), 3.96−4.09 (2H, m), 4.55 (2H, sept, J = 6.3 Hz), 6.46 (1H, s), 6.64 (1H, d, J = 1.2 Hz), 6.78 (1H, br), 6.92 (1H, d, J = 7.8 Hz), 7.11 (1H, d, J = 7.9 Hz), 7.21−7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.67, 20.16, 22.01, 22.10, 22.22, 22.31, 30.83, 45.90, 49.96, 51.57, 56.24, 69.79, 72.04, 72.89, 100.54, 108.33, 112.24, 117.79, 118.16, 122.10, 123.40, 126.28, 127.95, 128.53, 128.65, 135.17, 136.32, 136.65, 141.51, 153.82, 154.79, 155.15, 156.79; MS (EI) m/z 595 (1) [M^+], 580 (100)

(63) Owton, W. M.; Gallagher, P. T.; Juan-Montesinos, A. *Synth. Commun.* **1993**, *23*, 2119.

$[M^+ - CH_3]$], 538 (9); HRMS calcd for $C_{38}H_{46}NO_4$ 580.3427, found: 580.3422.

(B) From Korupensamine B (1b). To a suspension of **1b** (50.0 mg, 106 μmol) and K_2CO_3 (23.2 mg, 234 μmol) in 5 mL of acetone was added benzyl bromide (30 μL, 253 μmol) slowly over a period of 2.5 h at room temperature. The reaction mixture was purified by evaporation of the solvent in vacuo and subsequent chromatography on deactivated (7.5% NH_3)[8] silica gel (petroleum ether/ethyl acetate = 100:20 → 100:50). The crude product (11.2 mg, 24.0 μmol) and Cs_2CO_3 (23.6 mg, 71.9 μmol) and *i*-PrBr (6.72 μL, 71.9 μmol) were added in each case, after a total of 29 h the solvent was removed in vacuo, and the residue was filtered on deactivated (7.5% NH_3)[8] silica gel. The residue was dissolved in 1 mL of CH_2Cl_2 and after addition of *i*-PrBr (6.72 μL, 71.9 μmol), 1 mL of an aqueous KOH solution (5.0 n), and benzyltri-*n*-butylammonium chloride (1 mg) the reaction was stirred for 48 h at room temperature. The organic phase was separated and the aqueous phase was extracted several times with CH_2Cl_2. After evaporation of the solvent of the combined organic layers, the residue was purified by chromatography on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 100:0.1 → 100:5) to give **20b** (6.16 mg, 43%) as an amorphous solid. The compound was found to be identical with the material obtained above, from the total synthesis. $[\alpha]^{25}_D = +34.1$ (*c* 0.21, $CHCl_3$).

***N*-Benzylkorupensamine B (21b).** To a solution of **20b** (6.00 mg, 10.1 μmol) in 1 mL of dry CH_2Cl_2 was added BCl_3 (20.0 μL) at 0 °C. After stirring for 1 h at room temperature, MeOH was added and the solvent was removed under reduced pressure. Purification of the residue on deactivated (7.5% NH_3)[8] silica gel (CH_2Cl_2/MeOH = 100:3) afforded **21b** as a slightly yellow gum (3.22 mg, 68%): $[\alpha]^{24}_D = +86.3$ (*c* 0.35, MeOH); IR (KBr) ν 3600−3100, 2940, 2900, 1600, 1570 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.07 (3H, d, J = 6.5 Hz), 1.41 (3H, d, J = 6.7 Hz), 1.85 (1H, dd, J = 17.5 Hz, J = 4.1 Hz), 2.19 (1H, dd, J = 17.4 Hz, J = 11.2 Hz), 2.38 (3H, s), 3.33 (1H, d, J = 13.9 Hz), 3.33 (1H, m_c), 3.79 (1H, d, J = 13.9 Hz), 3.98 (1H, q, J = 6.7 Hz), 4.09 (3H, s), 6.34 (1H, s), 6.68 (1H, s), 6.85 (1H, s), 6.92 (1H, d, J = 7.9 Hz), 7.22−7.40 (6H, m), 9.52 (1H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.45, 19.32, 22.28, 30.32, 47.84, 50.53, 53.04, 56.26, 101.01, 107.00, 109.96, 114.00, 115.08, 116.87, 117.85, 121.30, 127.88, 128.50, 130.00, 131.48, 133.02, 135.74, 137.02, 153.25, 154.83, 155.16, 156.45; MS (EI) *m*/*z* 469 (1) [M^+], 454 (94) [$M^+ - CH_3$], 424 (11), 91 (100); HRMS calcd for $C_{30}H_{28}NO_4$ 454.2018, found: 454.2018.

Korupensamine B (1b). A mixture of **21b** (4.74 mg, 10.1 μmol) and 1.00 mg of Pd/C (10%) in 1 mL of dry MeOH was hydrogenated for 3 h under normal H_2 pressure. After filtration of the catalyst through Celite, the solvent was removed in vacuo. MPLC with MeOH/H_2O (8:2) at a pressure of 5 bar (10 mL/min) yielded **1b** as an amorphous, brown solid (2.76 mg, 72%): $[\alpha]^{23}_D = +70.3$ (*c* 0.09, MeOH) (lit.[3] +65, *c* 0.76, MeOH); IR (KBr) ν 3600−3200, 2940, 1600, 1570 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz) δ 1.13 (3H, d, J = 6.4 Hz), 1.59 (3H, d, J = 6.7 Hz), 2.09 (1H, dd, J = 17.4 Hz, J = 4.7 Hz), 2.30 (1H, dd, J = 17.2 Hz, J = 11.1 Hz), 2.31 (3H, s), 3.40 (1H, m_c), 4.03 (3H, s), 4.59 (1H, q, J = 6.7 Hz), 6.41 (1H, s), 6.75 (1H, s), 6.75 (1H, d, J = 7.7 Hz), 6.80 (1H, s), 7.02 (1H, d, J = 7.8 Hz); MS (EI) *m*/*z* 379 (6) [M^+], 364 (100) [$M^+ - CH_3$], 349 (9), 334 (27). The compound was found to be fully identical with an authentic sample of korupensamine B (**1b**) from *A. korupensis*.[3]

(1*R*,3*R*,5*P*)-*N*-Benzyl-5-(2′-hydroxymethyl-4′-isopropoxy-1′-phenyl)-6,8-diisopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (14a). The preparation of **14a** from **10a** (76%) was performed in analogy to the synthesis of **14b** described above: $[\alpha]^{24}_D = +157.8$ (*c* 0.32, $CHCl_3$); IR (KBr) ν 3600−3200, 2940, 2900, 1570 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (3H, d, J = 6.1 Hz), 1.09 (3H, d, J = 6.6 Hz), 1.18 (3H, d, J = 6.1 Hz), 1.23 (3H, d, J = 6.1 Hz), 1.30−1.40 (12H, m), 1.84 (1H, dd, J = 17.7 Hz, J = 10.9 Hz), 2.34 (1H, dd, J = 17.7 Hz, J = 4.6 Hz), 3.07 (1H, br), 3.18 (1H, d, J = 14.0 Hz), 3.41 (1H, m_c), 3.71 (1H, d, J = 13.9 Hz), 3.95 (1H, q, J = 6.6 Hz), 4.11 (1H, sept, J = 6.1 Hz), 4.22 (2H, br), 4.49 (1H, sept, J = 6.1 Hz), 4.63 (1H, sept, J = 6.1 Hz), 6.43 (1H, s), 6.89 (1H, dd, J = 8.3 Hz, J = 2.6 Hz), 7.00 (1H, d, J = 8.3 Hz), 7.07 (1H, d, J = 2.5 Hz), 7.16−7.35 (5H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.08, 20.23, 22.00, 22.05, 22.16, 31.09, 45.76, 50.04, 51.36, 64.73, 69.70, 69.84, 73.69, 101.19, 115.58, 116.55, 123.19, 126.34, 127.97, 128.62, 131.92, 133.49, 135.79, 140.94, 141.10, 153.72, 155.33, 157.17; MS (EI) *m*/*z* 531 (0.4) [M^+], 516 (49) [$M^+ - CH_3$], 474 (7), 414 (8), 91 (100); HRMS calcd for $C_{33}H_{42}NO_4$ 516.3114, found: 516.3111. Anal. Calcd for $C_{34}H_{45}NO_4$: C, 76.80; H, 8.53; N, 2.63. Found: C, 77.40; H, 8.37; N, 2.88.

(1*R*,3*R*,5*P*)-*N*-Benzyl-5-(2′-formyl-4′-isopropoxy-1′-phenyl)-6,8-diisopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (15a). The synthesis of **15a** from **14a** (90%) was achieved following the protocol for the preparation of **15b** from **14b** (see above): $[\alpha]^{23}_D = +151.7$ (*c* 0.35, $CHCl_3$); IR (KBr) ν 2940, 2900, 1670, 1570 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05−1.10 (9H, m), 1.24 (3H, d, J = 6.1 Hz), 1.32 (3H, d, J = 6.0 Hz), 1.35 (3H, d, J = 6.7 Hz), 1.40 (6H, d, J = 6.1 Hz), 1.95 (1H, dd, J = 17.3 Hz, J = 10.9 Hz), 2.27 (1H, dd, J = 17.5 Hz, J = 4.5 Hz), 3.21 (1H, d, J = 14.0 Hz), 3.41 (1H, m_c), 3.72 (1H, d, J = 14.1 Hz), 3.95 (1H, q, J = 6.7 Hz), 4.24 (1H, sept, J = 6.1 Hz), 4.51 (1H, sept, J = 6.0 Hz), 4.69 (1H, sept, J = 6.0 Hz), 6.39 (1H, s), 7.15−7.17 (2H, m), 7.21−7.36 (5 H, m), 7.48 (1H, d, J = 1.9 Hz), 9.65 (1H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.19, 20.22, 22.04, 22.11, 31.54, 45.78, 50.04, 51.37, 69.73, 70.02, 71.08, 98.31, 110.87, 118.69, 121.52, 123.07, 126.34, 127.97, 128.56, 133.27, 134.73, 135.36, 135.82, 141.08, 154.41, 155.86, 156.97, 193.16; MS (EI) *m*/*z* 529 (0.3) [M^+], 514 (48) [$M^+ - CH_3$], 472 (8), 430 (10), 91 (100); HRMS calcd for $C_{33}H_{40}NO_4$ 514.2957, found: 514.2959.

(1*R*,3*R*,5*P*)-*N*-Benzyl-5-(4′-hydroxy-2′-hydroxymethyl-5′-isopropoxy-8′-naphthyl)-6,8-diisopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (18a). The diol **18a** was synthesized from **15a** (41%) in analogy to the synthesis of **18b** from **15b** via **17b**: $[\alpha]^{21}_D = +74.5$ (*c* 0.40, $CHCl_3$); IR (KBr) ν 3600−3100, 2960, 2910, 1590, 1570 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (3H, d, J = 6.1 Hz, 1.00 (3H, d, J = 6.6 Hz), 1.02 (3H, d, J = 6.1 Hz), 1.29 (3H, d, J = 6.1 Hz), 1.34 (3H, d, J = 6.0 Hz), 1.37 (3H, d, J = 6.6 Hz), 1.55 (3H, d, J = 6.1 Hz), 1.56 (3H, d, J = 6.1 Hz), 1.96 (1H, dd, J = 17.8 Hz, J = 10.7 Hz), 2.12 (1H, dd, J = 17.6 Hz, J = 4.9 Hz), 3.26 (1H, d, J = 14.1 Hz), 3.35 (1H, m_c), 3.70 (1H, d, J = 14.3 Hz), 3.98 (1H, q, J = 6.7 Hz), 4.11 (1H, sept, J = 6.1 Hz), 4.55 (1H, sept, J = 6.4 Hz), 4.63 (2H, br), 4.91 (1H, sept, J = 6.0 Hz), 6.47 (1H, s), 6.82 (1H, s), 6.84 (1H, s), 6.87 (1H, d, J = 8.5 Hz), 7.16 (1H, d, J = 7.9 Hz), 7.21−7.38 (5H, m), 9.97 (1H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.25, 20.26, 22.04, 22.11, 22.21, 22.25, 22.36, 30.19, 45.76, 49.95, 51.62, 65.60, 69.60, 71.93, 72.78, 99.96, 106.45, 108.59, 114.53, 115.57, 121.61, 122.34, 126.33, 128.00, 128.12, 128.57, 129.30, 136.20, 136.40, 140.08, 141.26, 153.15, 154.79, 155.41, 155.50; MS (EI) *m*/*z* 597 (1) [M^+], 582 (30) [$M^+ - CH_3$], 516 (17), 91 (100); HRMS calcd for $C_{37}H_{44}NO_5$ 582.3219, found: 582.3219.

(1*R*,3*R*,5*P*)-*N*-Benzyl-5-(4′-hydroxy-5′-isopropoxy-2′-methyl-8′-naphthyl)-6,8-diisopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (19a). The preparation of **19a** from **18a** (63%) was performed in analogy to the synthesis of **19b** from **18b** reported above: $[\alpha]^{24}_D = +97.5$ (*c* 0.37, $CHCl_3$); IR (KBr) ν 3600−3100, 2950, 2900, 1580, 1570 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.90 (3H, d, J = 6.1 Hz), 1.00 (3H, d, J = 6.6 Hz), 1.03 (3H, d, J = 6.1 Hz), 1.29 (3H, d, J = 6.0 Hz), 1.34 (3H, d, J = 6.1 Hz), 1.38 (3H, d, J = 6.8 Hz), 1.54 (3H, d, J = 6.1 Hz), 1.55 (3H, d, J = 6.1 Hz), 2.00 (1H, dd, J = 17.6 Hz, J = 10.6 Hz), 2.14 (1H, dd, J = 17.6 Hz, J = 5.4 Hz), 2.30 (3H, s), 3.26 (1H, d, J = 14.2 Hz), 3.36 (1H, m_c), 3.72 (1H, d, J = 14.2 Hz), 3.99 (1H, q, J = 6.8 Hz), 4.09 (1H, sept, J = 6.0 Hz), 4.55 (1H, sept, J = 6.2 Hz), 4.90 (1H, sept, J = 6.2 Hz), 6.48 (1H, s), 6.62 (1H, br), 6.68 (1H, d, J = 1.4 Hz), 6.80 (1H, d, J = 8.1 Hz), 7.11 (1H, d, J = 7.9 Hz), 7.18−7.39 (5H, m), 9.86 (1H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.23, 20.40, 21.90, 22.05, 22.14, 22.25, 22.37, 30.07, 45.81, 49.98, 51.75, 69.55, 72.10, 72.63, 100.27, 105.56, 111.62, 114.32, 116.34, 121.64, 122.89, 126.33, 127.75, 128.00, 128.57, 136.30, 136.53, 137.15, 141.43, 153.19, 154.73, 154.85, 155.39; MS (EI) *m*/*z* 581 (1) [M^+], 566 (84) [$M^+ - CH_3$], 524 (13), 482 (8), 91 (100); HRMS calcd for $C_{37}H_{44}NO_4$ 566.3270, found: 582.3261.

(1*R*,3*R*,5*P*)-*N*-Benzyl-5-(5′-isopropoxy-4′-methoxy-2′-methyl-8′-naphthyl)-6,8-diisopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (20a). The synthesis of **20a** from **19a** (59%) was achieved following the protocol for the preparation of **20b** from **19b** described above: $[\alpha]^{21}_D = +99.6$ (*c* 0.35, $CHCl_3$); IR (KBr) ν 2940, 2900, 1560 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (3H, d, $J = 6.1$ Hz), 0.97 (3H, d, $J = 6.1$ Hz), 0.99 (3H, d, $J = 6.6$ Hz), 1.29 (3H, d, $J = 6.1$ Hz), 1.34 (3H, d, $J = 6.1$ Hz), 1.38 (3H, d, $J = 6.7$ Hz), 1.43 (6H, d, $J = 6.0$ Hz), 1.98 (1H, dd, $J = 17.6$ Hz, $J = 10.7$ Hz), 2.14 (1H, dd, $J = 17.8$ Hz, $J = 5.1$ Hz), 2.33 (3H, s), 3.26 (1H, d, $J = 14.0$ Hz), 3.31 (1H, m_c), 3.72 (1H, d, $J = 14.3$ Hz), 3.96 (3H, s), 3.96−4.08 (2H, m), 4.50−4.68 (2H, mult), 6.46 (1H, s), 6.64 (1H, d, $J = 1.4$ Hz), 6.74 (1H, brs), 6.93 (1H, d, $J = 7.8$ Hz), 7.16 (1H, d, $J = 7.8$ Hz), 7.21−7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.26, 20.37, 22.02, 22.08, 22.21, 22.37, 30.04, 45.76, 49.90, 51.75, 56.20, 69.46, 72.42, 72.92, 100.83, 108.20, 112.38, 117.85, 117.95, 121.74, 123.68, 126.30, 127.98, 128.32, 128.47, 128.56, 135.23, 136.56, 136.79, 141.47, 153.79, 154.85, 155.26, 156.94; MS (EI) *m*/*z* 595 (3) [M^+], 580 (100) [$M^+ - CH_3$], 538 (17), 496 (11), 91 (74); HRMS calcd for $C_{38}H_{46}NO_4$ 580.3427, found: 580.3425.

Korupensamine A (1a). The *N*- and *O*-deprotection of **20a** to give **1a** (71%) was performed in analogy to the synthesis of **1b** presented above: $[\alpha]^{25}_D = -72.3$ (*c* 0.04, MeOH) (*c* 0.09, MeOH) (lit.[3] −75.5, *c* 1.84, MeOH); IR (KBr) ν 3600−3200, 2940, 1590, 1570 (m, C═C) cm^{-1}; ^1H NMR (CD_3OD, 200 MHz) δ 0.95 (3H, d, $J = 6.3$ Hz), 1.46 (3H, d, $J = 6.6$ Hz), 1.74 (1H, dd, $J = 16.9$ Hz, $J = 10.7$ Hz), 2.27 (1H, dd, $J = 17.2$ Hz, $J = 4.1$ Hz), 2.28 (3H, s), 3.18 (1H, m_c), 4.06 (3H, s), 4.39 (1H, q, $J = 6.6$ Hz), 6.34 (1H, s), 6.73 (1H, s), 6.75 (1H, s), 6.80 (1H, d, $J = 8.0$ Hz), 7.07 (1H, d, $J = 7.8$ Hz); MS (EI) *m*/*z* 379 (8) [M^+], 378 (9) [$M^+ - H$], 364 (100) [$M^+ - CH_3$], 349 (7), 334 (27). The compound obtained was found to be fully identical with an authentic sample of korupensamine A (**1a**) from *A. korupensis*.[3]

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Supporting Information Available: ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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