Pergamon

Tetrahedron 54 (1998) 497–512

TETRAHEDRON

First Synthesis of the Antimalarial Naphthylisoquinoline Alkaloid Dioncophylline C, and its Unnatural Anti-HIV Dimer, Jozimine C[1]

Gerhard Bringmann*, Jörg Holenz, Ralf Weirich, Martin Rübenacker, and Christian Funke

Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany

Michael R. Boyd and Robert J. Gulakowski

Laboratory of Drug Discovery Research and Development, National Cancer Institute, Building 1052, Room 121, Frederick, MD 21702-1201, USA

Guido François

Prins Leopold Instituut voor Tropische Geneeskunde, Nationalestraat 155, B-2000 Antwerpen, Belgium

Received 9 October 1997; accepted 3 November 1997

Abstract: The first total synthesis of dioncophylline C, a new antimalarial lead structure, is described. For the directed construction of the stereogenic biaryl axis, the 'lactone methodology' is applied, despite the lack of a 'bridgehead oxygen' function in the target molecule. Furthermore, the novel dimer of dioncophylline C, 'jozimine C', is prepared, by oxidative phenolic coupling of the protected natural monomer. Jozimine C displays good antimalarial activity (*Plasmodium falciparum*; IC_{50} = 0.445 µg/ml), and, in particular, represents the first unnatural dimer of a naphthylisoquinoline alkaloid with a high anti-HIV activity (HIV-1; EC_{50} = 27 µg/ml).

INTRODUCTION

Dioncophylline C (**1**) from the West-African vine *Triphyophyllum peltatum* (Dioncophyllaceae)[2] is the as yet most active antimalarial naphthylisoquinoline alkaloid.[3,4] Its *in vitro* activity (IC_{50} = 0.014 µg/ml)[4] against *Plasmodium falciparum*, the pathogenic agent of the severe *malaria tropica*, is in the range of medically used drugs (*e.g.* artemether in the same test system: IC_{50} = 0.014 µg/ml[5]). Moreover, it exhibits excellent *in vitro*[4] and *in vivo*[6] activities against the rodent malaria parasite *P. berghei*, while displaying no direct lethal (OF1 mice) and only very low cytotoxic (MRC-5 and P388) effects.[6] For these reasons, dioncophylline C (**1**) can be regarded as a promising novel antimalarial lead structure and thus constitutes an attractive synthetic goal.

Besides dioncophylline C, itself, also its (as yet unknown) dimer **4** is of great interest. Previous work of our group[7] showed jozimine A (**6**), the unnatural dimer of the naturally occurring[8] (but likewise synthetically available[9]) naphthylisoquinoline alkaloid dioncophylline A (**3**) to exhibit antimalarial activity *ca.* 20 times higher than its monomer. The same effect was observed for jozimine B,[10] the artificial dimer of the natural[2] alkaloid ancistrocladine (**9**, see Scheme 1) and even for dimers of unnatural analogs.[11] Thus, transformation of

0040-4020/98/$19.00
PII: S0040-4020(97)10301-5

the as yet most active naphthylisoquinoline alkaloid, dioncophylline C (**1**), into its dimer **4**, 'jozimine C', might give rise to a still more active new antimalarial compound. Moreover, the close structural similarity of **4** with the michellamines, *e.g.* michellamine B (**5**),[12] a natural 'mixed dimer' of atropisomeric korupensamines A (**2a**) and B (**2b**),[13] makes the synthesis of **4** even more rewarding: Michellamines are promising novel anti-HIV alkaloids from the Cameroonian liana *Ancistrocladus korupensis* (Ancistrocladaceae). Their clinical use, however, is hampered by a distinct cytotoxicity,[12] making the need for better structural analogs evident.

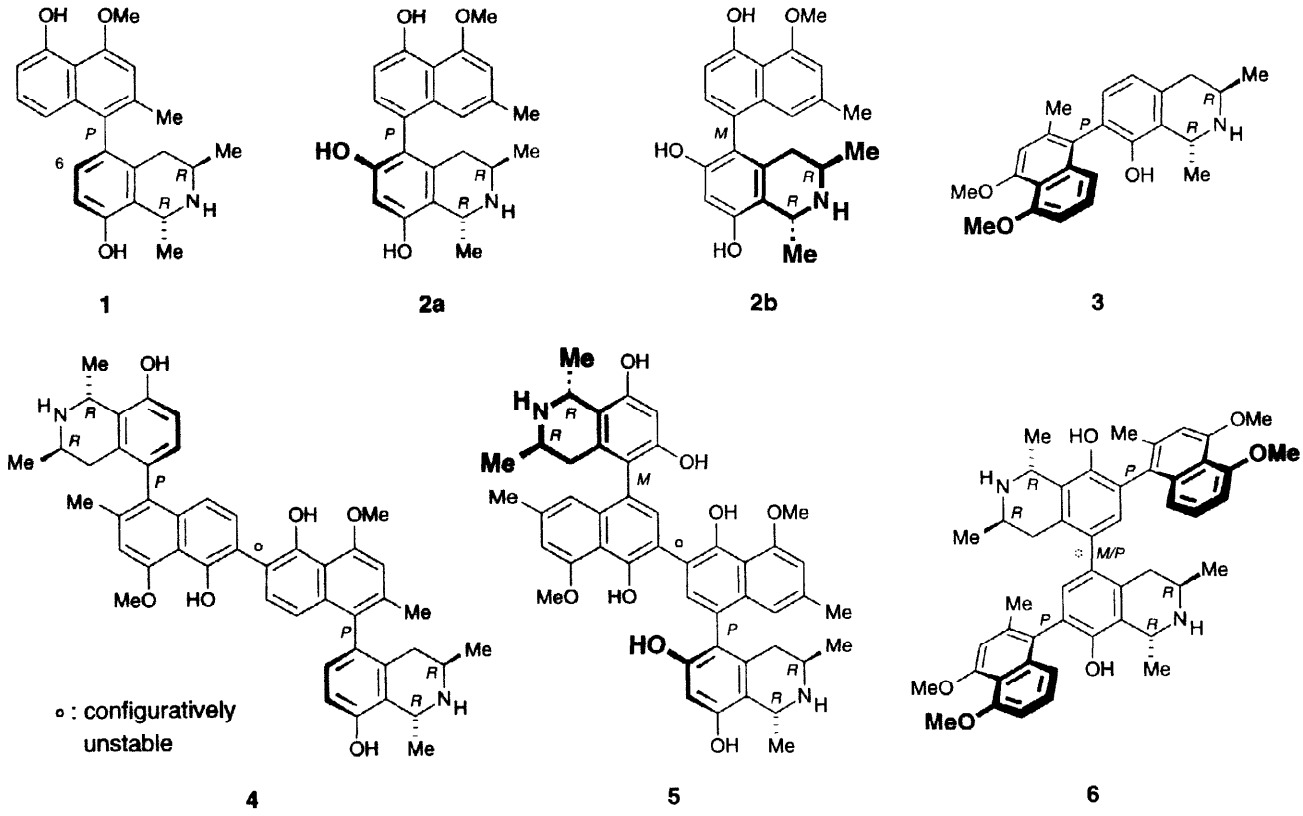


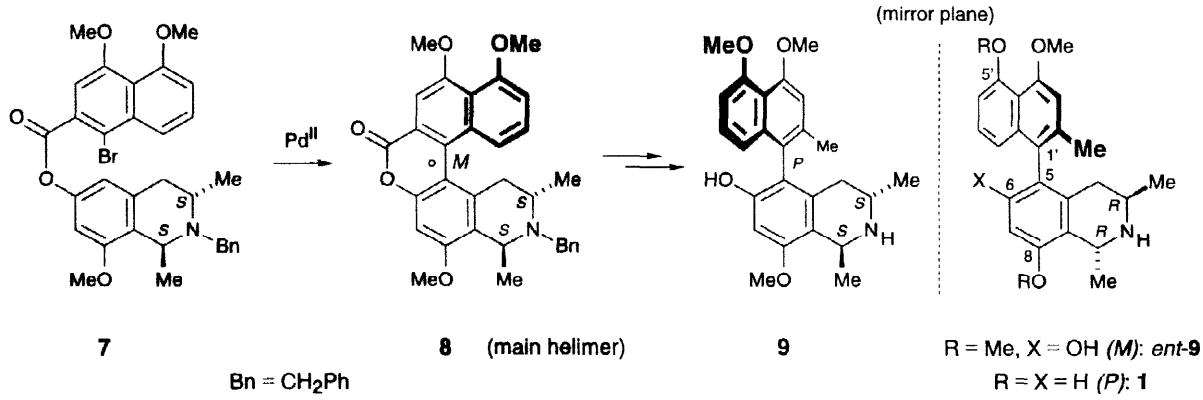
Fig. 1. Pharmacologically active mono- and dimeric naphthylisoquinolines.

In this paper, we describe the first total synthesis of dioncophylline C (**1**), and its oxidative dimerization to give jozimine C (**4**). Part of the work has previously been reported in preliminary form.[3,10] More recent attemps to synthesize **1**, by intermolecular biaryl coupling strategies, have not succeeded as yet.[14]

RESULTS AND DISCUSSION

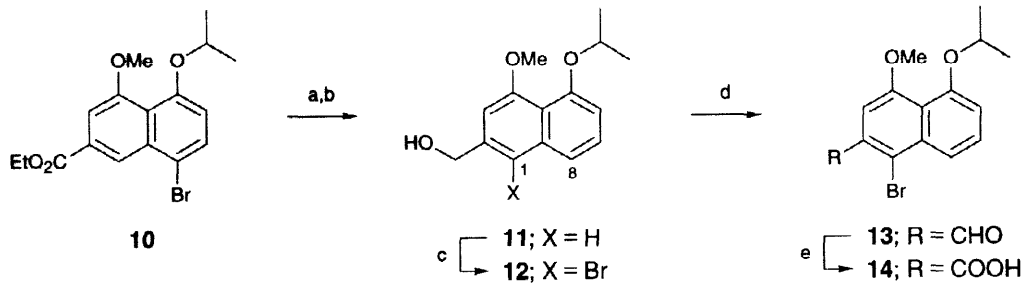
With its 5,1'-position of the biaryl axis, dioncophylline C (**1**) is structurally related to ancistrocladine (**9**) - in fact it is an 8- and 5'-*O*-demethylated and 6-deoxygenated analog of the enantiomer of **9**. Ancistrocladine was the first naphthylisoquinoline alkaloid ever prepared,[15] including the regio- and stereocontrolled

construction of the biaryl synthesis by our 'lactone methodology',[16] by *intra*molecular biaryl coupling of **7** to give the configuratively unstable biaryl lactone **8**, predominantly with the desired *M*-configuration at the biaryl axis. Its ring cleavage and further transformation gave stereochemically homogeneous ancistrocladine (**9**). Due to the efficiency of this methodology, we embarked on the first total synthesis of dioncophylline C by a similar concept, but starting from specifically *O*-protected naphthalene and isoquinoline precursors for the final generation of free phenolic OH-functions at C-8 and C-5', from *R,R*- (instead of *S,S*-) enantiomeric material, and envisaging the eventual reductive elimination of a transiently required 'bridgehead' oxygen function at C-6.



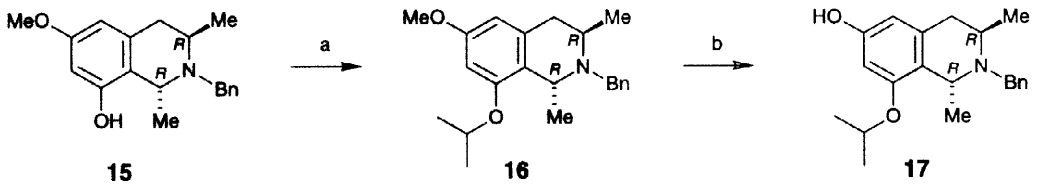
Scheme 1. Key features of the total synthesis of ancistrocladine (**9**) *via* the configuratively unstable biaryl lactone **8**,[15] and structural comparison of **9** with the target molecule, dioncophylline C (**1**).

The synthesis of the required naphthalene precursor **14** (Scheme 2) started with **10**, a building block previously used for the first total synthesis of the 5,8'-coupled korupensamines and michellamines.[17] For the preparation of the 5,1'-coupled alkaloid dioncophylline C, the halogen thus had to be removed and, after reduction to the alcohol **11**, to be introduced into the required 1-position to give **12**, followed by renewed (stepwise) oxidation to the naphthalene coupling moiety **14** in good overall yields (80%).



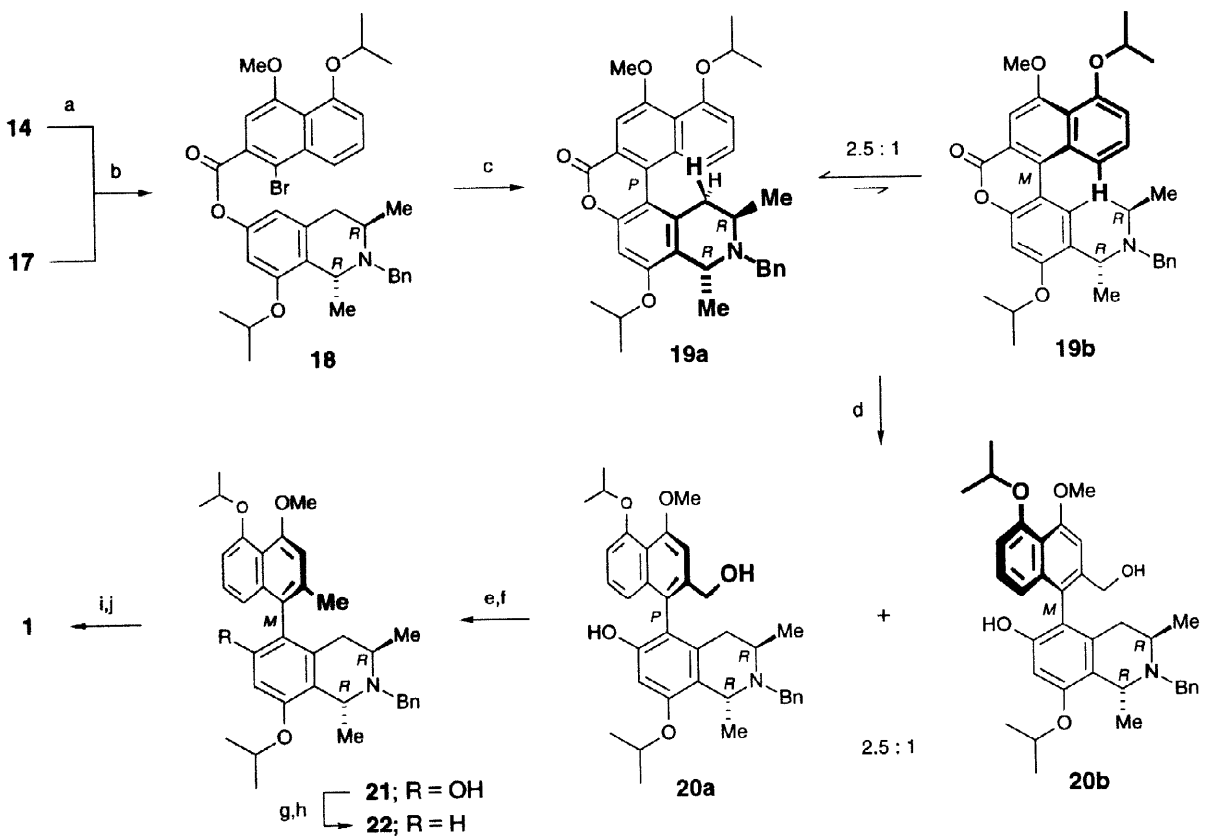
Scheme 2. Reagents and conditions: a) Pd/C (10%), H_2, Et_3N, MeOH; b) $LiAlH_4$, THF, 93% from **10**; c) $N(n\text{-}Bu)_4Br_3$, NaOAc, CH_2Cl_2, 95%; d) MnO_2, CH_2Cl_2, 90%; e) $NaClO_2$, NH_2SO_3H, NaOAc, HOAc, H_2O, dioxan, 98%.

The tetrahydroisoquinoline moiety **17** was prepared from the known[18] enantiomerically pure building block **15**, by *O*-isopropylation and selective cleavage of the methyl ether (Scheme 3).



Scheme 3. Reagents and conditions: a) *i*-C_3H_7Br, PTC, 2 N NaOH, CH_2Cl_2, 7 d, 87%; b) *i*-C_3H_7SNa, DMF, 68%.

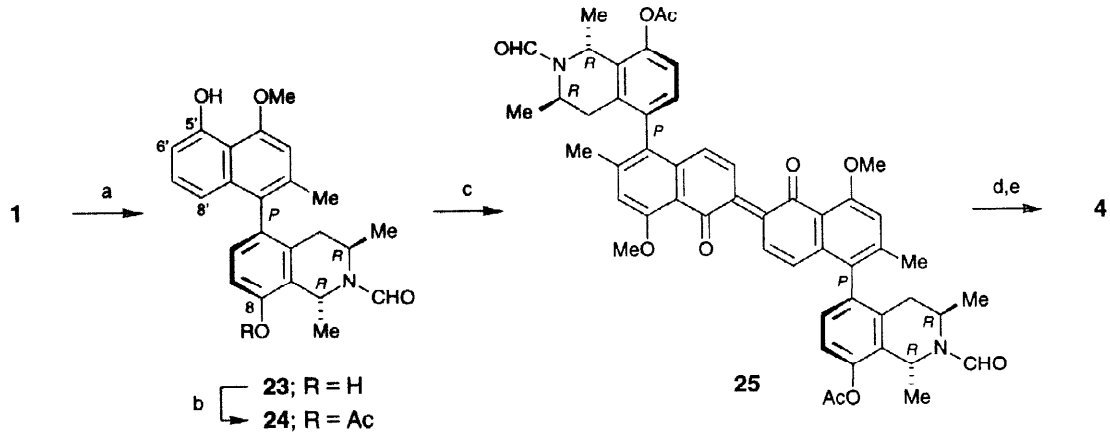
Prefixation of **14** (*via* its acid chloride) and **17** by esterification to give **18** and Pd-catalyzed intramolecular biaryl coupling (Scheme 4) regiospecifically led to the 5-coupled biaryl **19**, exclusively, no hints being obtained at a likewise imaginable 7-coupling. The two helicene-like distorted diastereomers, **19a** and **19b**, interconvert at room temperature, with an atropisomeric ratio of 2.5 : 1 in favor of the desired *P*-helical form **19a**.[19] With conservation of this diastereomeric ratio, reductive ring cleavage yielded the atropoisomeric alcohols **20a** and **20b**, which are now configuratively stable at the biaryl linkage and were easily be separated at this point. Conversion of **20a** into the methyl compound **21** by hydroxy/halogen exchange and subsequent



Scheme 4. Reagents and conditions: a) $(COCl)_2$, CH_2Cl_2; b) Hünig's base, DMAP, CH_2Cl_2, 71% from **14**; c) $(Ph_3P)_2PdCl_2$, NaOAc, DMA, 100 °C, 69%; d) $LiAlH_4$, THF, 81%; e) Ph_3P, $C_2Br_2Cl_4$, CH_2Cl_2[20]; f) $LiAlH_4$, THF, 0 °C, 95% from **20a**; g) Tf_2O, $Tl(OEt)_3$, CH_2Cl_2; h) $(Ph_3P)_2PdCl_2$, dppp, *n*-Bu_3N, HCO_2H, DMF, 100 °C, 68% from **21**; i) BCl_3, CH_2Cl_2, -40 °C; j) Pd/C (10%), H_2, MeOH, 94% from **22**.

LAH reduction, followed by reductive elimination of the OH-group at C-6 *via* the corresponding *O*-triflate,[2] and removal of the protective groups finally gave dioncophylline C (**1**) in good yields, identical in all respects with an authentic sample from *T. peltatum*.[2] Dioncophylline C (**1**) is the first naphthylisoquinoline alkaloid without an oxygen function next to the biaryl axis ever synthesized, showing the broad applicability of the lactone methodology even in such particular cases.

For the chemical[21] dimerization of the now synthetically available dioncophylline C (**1**), the methodology developed in the first synthesis of michellamines[22,17] was applied, by *N*-formylation and specific *O*-acetylation of the non-chelated oxygen function at C-8 (Scheme 5). The specifically monophenolic dioncophylline C derivative **24** thus obtained was then submitted to phenoloxidative conditions using silver(I) oxide, giving the violet-colored dione **25**. Compared with the almost quantitative dimerization step in the synthesis of michellamines,[22] the yields are somewhat lower here, apparently due to the now free aromatic position at C-8.[23] Photoreduction[17] of **25** and cleavage of all of the protective groups in a single step finally led to dimeric dioncophylline C (**4**), subsequently named jozimine C.



Scheme 5. Reagents and conditions: a) $(CH_3)_3CCO_2CHO$, CH_2Cl_2, 20 °C, 98%; b) AcCl, Et_3N, cat. DMAP, CH_2Cl_2, 97%; c) Ag_2O, 0.2% Et_3N in $CHCl_3$, 40%; d) MeOH, incandescent light; e) MeOH/HCl, reflux, 67% from **25**.

Regrettably, the dimerization of dioncophylline C (**1**) does not lead to better antimalarial activities - jozimine C (**4**) was found to be distinctly less active (IC_{50} = 0.445 μg/ml) than **1**, even though **4** is still quite a potent antiplasmodial agent. This decrease in activity may have to do with the structural similarity to the michellamines, the naturally occurring dimers of the likewise antimalarial korupensamines (**2a**,**2b**): Michellamines, *e.g.* **5**, are virtually inactive towards *P. falciparum*. On the other hand, the structural relationship to michellamines makes understandable that jozimine C (**4**) has an appreciable anti-HIV activity (HIV-1; EC_{50} = 27 μg/ml), nearly as good as michellamine B (EC_{50} = 14 μg/ml in the same test system). Like michellamines, **4** shows a distinct cytotoxicity (IC_{50} = 64 μg/ml), so that the therapeutic concentration range is again quite limited. Still, jozimine C actually is the as yet most anti-HIV active unnatural dimer of a natural

monomeric naphthylisoquinoline alkaloid ever synthesized and gives valuable information on structure-activity relationships of this important class of dimeric naphthylisoquinolines.

The first total synthesis of the highly antimalarial alkaloid dioncophylline C (**1**) and its dimerization to its as yet unknown[24] dimer **4** (jozimine C) underlines the efficiency of the synthetic methods developed for the preparation of such bi- and quateraryl target molecules, the 'lactone methodology' and the oxidative dimerization after specifically sealing the *O*- and *N*-functionalities of the isoquinoline part. Furthermore it is shown that dimerization of naphthylisoquinolines, in particular if leading to naphthalene-linked dimers, does not necessarily improve antimalarial activities. Finally, the good anti-HIV activity of **4** shows that it is now rewarding to prepare more such unnatural dimers of natural- or unnatural - monomeric naphthylisoquinolines for biological testing. This work is in progress.

EXPERIMENTAL

All moisture-sensitive reactions were carried out under an argon atmosphere. Solvents were dried and purified by conventional methods prior to use. Melting points were measured on a Reichert-Jung Thermovar hot-plate and are uncorrected. NMR spectra were recorded with a Bruker AC 200, a Bruker WM 400, and a Bruker DMX 600 spectrometer. The chemical shifts δ are given in parts per million (ppm) with the proton signals in the deuterated solvent as internal reference for ^{1}H and ^{13}C NMR. The coupling constants, *J*, are given in Hertz. HPLC separations: combination of a Waters M 510 HPLC pump, a U6K injector, and an amino-bonded Rainin-Dynamax-60A column. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. CD spectra were determined on a Jobin Yvon Model CD6 instrument. IR spectra were taken on a Perkin-Elmer 1420 infrared spectrophotometer and reported in wave numbers (cm^{-1}). Mass spectra were obtained on a Finnigan MAT 8200 and a Finnigan MAT 90 mass spectrometer at 70 eV in the EI mode unless otherwise stated. High resolution mass spectra were recorded on the last-mentioned instrument. Elemental analyses were performed by the Microanalytical Laboratory of the University of Würzburg on a LECO CHNS-932 instrument. Michellamine B (**5**) was available from previous isolation work.[12]

General Procedures. - 1. Transformation of Amines into Hydrobromides and Hydrochlorides: To a solution of the substrate in methanol 47% hydrobromic or hydrochloric acid was carefully added at 0 °C until a pH of approx. 6-7 was reached. After evaporation of the solvent *in vacuo* the residue was recrystallized from the stated solvent. **- 2. Generation of the Free Bases from the Corresponding Hydrohalides:** A solution of the salt in methanol was adjusted to approx. pH = 10 using concd. ammonia. The solution was concentrated *in vacuo* and the residue was filtered over Al_2O_3 with CH_2Cl_2 or CH_2Cl_2 / methanol as the eluent.

2-Hydroxymethyl-5-isopropoxy-4-methoxynaphthalene (11). A solution of **10**[17] (12.0 g, 33.9 mmol) and Et_3N (3.53 g, 35.0 mmol) in methanol (300 ml) was hydrogenated in the presence of Pd/C (10%, 400 mg) for 15 h in a Parr-equipment at high pressure (5 bar). After filtration and evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and washed with hydrochloric acid (2 N) and H_2O (50 ml each). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. A solution of the resulting oil in dry THF (250 ml) was cautiously treated with $LiAlH_4$ (1.27 g, 33.6 mmol) in portions and the mixture was heated to reflux for 1.5 h. After addition of hydrochloric acid (half concd., 10 ml), stirring was continued for 1 h and the aqueous layer was extracted with Et_2O (3 × 250 ml). The combined organic layers were washed with satd. aqueous K_2CO_3 and H_2O, then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from petroleum ether to give **11** (7.77 g, 93%) as colorless crystals: mp 69 °C; IR (KBr): $\tilde{\nu}$ 3360, 2950, 2900, 1560, 1260, 825, 745; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 [d, *J* = 6.0, 6H, $CH(CH_3)_2$], 3.79 (s, 3H, 4-OCH_3), 4.46 [sept, *J* = 6.0, 1H, $CH(CH_3)_2$], 4.60 (s, 2H, 2-CH_2OH), 6.64 (s, 1H, 3-H), 6.80-6.89 (m, 1H, 6-H, 7-H or 8-H), 7.11 (s, 1H, 1-H), 7.21-7.31 (m, 2H, 6-H, 7-H or 8-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7 [$CH(CH_3)_2$], 55.7 (4-OCH_3), 64.5 (CH_2OH), 73.1 [$CH(CH_3)_2$], 104.8, 113.0, 117.8, 118.8, 121.6, 126.1, 137.0, 138.8, 154.2, 156.6; MS: *m/z* (%) = 246 (39) [M^+], 204 (100) [M^+ - C_3H_6], 189 (29) [M^+ - C_3H_6 - CH_3]; Anal. calcd. for $C_{15}H_{18}O_3$ (246.3): C, 73.14; H, 7.36. Found: C, 73.21; H, 7.40.

1-Bromo-2-hydroxymethyl-5-isopropoxy-4-methoxynaphthalene (12). To a cooled (0 °C) mixture of **11** (5.00 g, 20.3 mmol) and NaOAc (8.33 g, 101 mmol) in CH_2Cl_2 (200 ml) a solution of $N(n\text{-}Bu)_4Br_3$ (11.76 g, 24.4 mmol) in CH_2Cl_2 (250 ml) was added dropwise over a period of 30 min and stirring was continued for further 30 min. The reaction mixture was allowed to warm up to room temperature and Na_2SO_3 solution (80 ml, 2 N) was added. The organic layer was washed with H_2O (3 × 250 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on silica gel with petroleum ether / ethyl acetate (3:1) and recrystallization from Et_2O / petroleum ether gave **12** (6.27 g, 95%); mp 94.5 °C; IR (KBr): $\tilde{\nu}$ 3280, 2980, 2920, 1580, 1560, 1260, 1065, 750; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 [d, *J* = 6.1, 6H, $CH(CH_3)_2$], 3.85 (s, 3H, 4-OCH_3), 4.51 [m_c, 1H, $CH(CH_3)_2$], 4.83 (s, 2H, 2-CH_2OH), 6.91 (s, 1H, 3-H), 6.95 (dd, *J* = 7.8, 1.0, 1H, Ar-H), 7.41 (t, *J* = 7.7, 1H, 7-H), 7.88 (dd, *J* = 8.6, 1.1, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0 [$CH(CH_3)_2$], 56.2 (4-OCH_3), 65.7 (CH_2OH), 73.4 [$CH(CH_3)_2$], 105.9, 112.6, 113.4, 119.8, 120.4, 127.6, 138.3, 155.0, 156.8; MS: *m/z* (%) = 326/324 (36/35) [M^+], 284/282 (100/98) [M^+ - C_3H_6]; Anal. calcd. for $C_{15}H_{17}BrO_3$ (325.2): C, 55.40; H, 5.26. Found: C, 55.79; H, 5.57.

1-Bromo-5-isopropoxy-4-methoxynaphthalene-2-carbaldehyde (13). A mixture of **12** (2.17 g, 6.67 mmol) and activated MnO_2 (10.0 g) in CH_2Cl_2 (200 ml) was refluxed for 1.5 h. Inorganic insoluble materials were filtered off and the filtrate was washed with a satd. K_2CO_3 solution and dried ($MgSO_4$). The solvent was

removed *in vacuo* to yield **13** (1.93 g, 90%) as yellow crystals (CH_2Cl_2); mp 98 °C; IR (KBr): $\tilde{\nu}$ 1670, 1585, 1260, 1060, 750; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.41 [d, J = 6.0, 6H, $CH(CH_3)_2$], 3.99 (s, 3H, 4-OCH_3), 4.56 [m_c, 1H, $CH(CH_3)_2$], 7.17 (dd, J = 5.7, 0.7, 1H, 6-H), 7.25 (s, 1H, 3-H), 7.56 (t, J = 7.8, 1H, 7-H), 8.18 (dd, J = 8.6, 1.0, 1H, 8-H), 10.62 (s, 1H, 3-CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9 [$CH(CH_3)_2$], 56.0 (4-OCH_3), 73.6 [$CH(CH_3)_2$], 102.5, 116.5, 121.4, 122.3, 128.4, 131.4, 135.3, 155.5, 157.3, 192.9 (CHO); MS: *m/z* (%) = 324/322 (33/32) [M^+], 282/280 (100/98) [M^+ - C_3H_6], 267/265 (33/32) [M^+ - C_3H_6 - CH_3], 239/237 (17/16) [M^+ - C_3H_6 - CH_3 - CHO]; Anal. calcd. for $C_{15}H_{15}BrO_3$ (323.2): C, 55.74; H, 4.67. Found: C, 55.98; H, 4.78.

1-Bromo-5-isopropoxy-4-methoxy-2-naphthoic acid (14). To a solution of **13** (1.93 g, 5.97 mmol) in dioxan (200 ml), glacial acetic acid (42 ml, 670 mmol) and the solutions of NaOAc (21.0 g, 155 mmol) in H_2O (42 ml), sulphamic acid (1.14 g, 11.7 mmol) in H_2O (42 ml) and $NaClO_2$ (1.01 g, 11.7 mmol) in H_2O (42 ml) were added consecutively. After stirring for 4 h at room temperature, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (250 ml), washed with H_2O (3 × 200 ml) and dried (K_2CO_3). Evaporation of the solvent and recrystallization of the crude product from Et_2O / petroleum ether afforded **14** (1.99 g, 98%) as orange-red crystals; mp 179 °C; IR (KBr): $\tilde{\nu}$ 1675, 1570, 1250; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.41 [d, J = 6.0, 6H, $CH(CH_3)_2$], 3.99 (s, 3H, 4-OCH_3), 4.57 [m_c, 1H, $CH(CH_3)_2$], 7.10 (d, J = 7.9, 1H, 6-H), 7.20 (s, 1H, 3-H), 7.54 (t, J = 8.4, 1H, 7-H), 8.16 (d, J = 8.6, 1H, 8-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0 [$CH(CH_3)_2$], 56.4 (4-OCH_3), 73.6 [$CH(CH_3)_2$], 106.3, 114.3, 115.2, 121.8, 122.4, 128.4, 130.0, 135.7, 155.2, 156.7, 172.2 (COOH); MS: *m/z* (%) = 340/338 (28/27) [M^+], 298/296 (100/98) [M^+ - C_3H_6], 283/281 (36/35) [M^+ - C_3H_6 - CH_3], 255/253 (15/14) [M^+ - C_3H_6 - CH_3 - CHO]; Anal. calcd. for $C_{15}H_{15}BrO_4$ (339.2): C, 53.11; H, 4.45. Found: C, 53.24; H, 4.41.

(1*R*,3*R*)-*N*-Benzyl-6-methoxy-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (16). A solution of **15**[18] (2.50 g, 8.41 mmol) in CH_2Cl_2 was treated with sodium hydroxide (100 ml, 2 N), tri-*n*-butylammonium chloride (400 mg), and isopropyl bromide (3.10 g, 25.0 mmol). After stirring for 7 d at room temperature the aqueous laver was extracted exhaustively with CH_2Cl_2 and the collected organic phases were dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was filtered over deactivated (5% NH_3) silica gel with CH_2Cl_2 / methanol (100:3) as the eluent, to afford **16** (2.48 g, 87%) as an oil. It was characterized as its HBr salt, which was recrystallized from isopropanol / Et_2O to give colorless crystals; mp 218-220 °C; $[\alpha]_D^{25}$ = +24.2 (c = 0.54 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 2960 , 2920, 2650-2500, 1600, 1150; ^{1}H NMR (200 MHz, MeOH-d_4): δ = 1.32 [d, J = 6.6, 6H, $CH(CH_3)_2$], 1.53 (d, J = 6.6, 3H, 3-CH_3), 1.74 (d, J = 6.6, 3H, 1-CH_3), 3.08 (dd, J = 19.0, 12.2, 1H, 4-H_{ax}), 3.28 (dd, J = 19.0, 5.8, 1H, 4-H_{eq}), 3.53 (m_c, 1H, 3-H), 3.83 (d, J = 13.2, 1H, NCHHPh), 3.87 (s, 3H, OCH_3), 4.34 [sept, J = 6.6, 1H, $CH(CH_3)_2$], 4.64 (d, J =

13.2, 1H, NCH*H*Ph), 4.73 (q, *J* = 6.6, 1H, 1-H), 6.50 (s, 1H, 5-H or 7-H), 6.55 (s, 1H, 5-H or 7-H), 7.33 (m, 2H, Ar-H), 7.53 (m, 3H, Ar-H); MS: *m/z* (%) = 339 (0.5) [M^+], 324 (100) [M^+ - CH_3], 282 (42) [M^+ - CH_3 - C_3H_7 + H], 91 (66) [$C_7H_7^+$]; Anal. calcd. for the HBr salt $C_{22}H_{30}BrNO_2$ (420.4): C, 62.86; H, 7.19; N, 3.33. Found: C, 63.11; H, 7.13; N, 3.07.

(1*R*,3*R*)-*N*-Benzyl-6-hydroxy-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (17). To a solution of **16** (1.50 g, 4.42 mmol) in dry DMF (150 ml) sodium thioisopropylate[25] (1.96 g, 20.0 mmol) was added and then heated to reflux for 3 h. The reaction mixture was allowed to cool down to room temperature and poured into hydrochloric acid (600 ml, 2 N). After several extractions with CH_2Cl_2, the combined organic lavers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was converted into the free base and purified by flash chromatography on deactivated (2.5% NH_3) silica gel with CH_2Cl_2 / methanol (100:1) as the eluent to afford crude **17** (978 mg, 68%) and starting material **16** (120 mg, 8%). The main product **17** was characterized as its HBr salt after recrystallization from isopropanol / Et_2O; mp 292-294 °C; $[\alpha]_D^{25}$ = +49.8 (*c* = 0.45 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3450, 2960, 2920, 2750-2600, 1600, 1150; ^{1}H NMR (200 MHz, MeOH-d_4): δ = 1.32 [d, *J* = 6.0, 6H, CH(C*H*$_3$)$_2$], 1.52 (d, *J* = 6.7, 3H, 3-CH_3), 1.72 (d, *J* = 6.7, 3H, 1-CH_3), 3.18 (m, 2H, 4-H), 3.51 (m_c, 1H, 3-H), 3.85 (d, *J* = 13.1, 1H, NC*H*HPh), 4.32 (q, *J* = 6.7, 1H, 1-H), 4.63 [m, 2H, C*H*(CH$_3$)$_2$ and NCH*H*Ph], 6.36 (d, *J* = 2.1, 1H, 5-H), 6.43 (d, *J* = 2.1, 1H, 7-H), 7.30 (m, 2H, Ar-H), 7.52 (m, 3H, Ar-H); MS: *m/z* (%) = 325 (1) [M^+], 324 (6) [M^+ - H], 311 (27) [M^+ - CH_3], 310 (84) [M^+ - CH_3 - H], 268 (39) [M^+ - CH_3 - C_3H_7 + H], 91 (100) [$C_7H_7^+$]; Anal. calcd. for HBr salt $C_{21}H_{28}BrNO_2$ (407.2): C, 61.95; H, 6.93; N, 3.44. Found: C, 62.15; H, 7.38; N, 4.03.

(1*R*,3*R*)-(*N*-Benzyl-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl) 1'-Bromo-5'-isopropoxy-4'-methoxy-2'-naphthoate (18). To a suspension of **14** (651 mg, 1.92 mmol) in dry CH_2Cl_2 (25 ml) and a catalytic amount of DMF (approx. 10 µl), oxalyl chloride (185 µl, 2.11 mmol) was added and the mixture was stirred for additonal 30 min at room temperature. The yellow reaction mixture was added dropwise to a solution of **17** (595 mg, 1.83 mmol), *N,N*-diisopropylethylamine (Hünig's base) (523 µl, 3.00 mmol) and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) (4 mg) in dry CH_2Cl_2. After completion of the reaction (TLC), the solvent was removed *in vacuo* and the residue was purified by flash chromatography on deactivated (2.5% NH_3) silica gel with CH_2Cl_2 / petroleum ether (2:1), to yield **18** (840 mg, 71%) as colorless crystals; mp 55 °C; $[\alpha]_D^{20}$ = +45.5 (*c* = 0.52 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 2960, 2920, 1740, 1580; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15-1.48 [m, 18H, 1-CH_3, 3-CH_3 and 2 CH(C*H*$_3$)$_2$], 2.68 (m, 2H, 4-H), 3.28 (d, *J* = 14.0, 1H, NC*H*HPh), 3.55 (m_c, 1H, 3-H), 3.85 (d, *J* = 14.0, 1H, NCH*H*Ph), 3.96 (q, *J* = 6.7, 1H, 1-H), 4.00 (s, 3H, OCH_3), 4.56 [sept, *J* = 6.1, 2H, 2 C*H*(CH$_3$)$_2$], 6.62 (d, *J* = 2.2, 1H, 5-H), 6.67 (d, *J* = 2.2, 1H, 7-H), 7.11 (d, *J* = 7.6, 1H, 6'-H), 7.17 (s, 1H, 3'-H), 7.21-7.40 (m, 5H, Ar-H), 7.58 (t, *J* = 7.9, 1H, 7'-H), 8.15 (d, *J* = 7.6, 1H,

8'-H); MS (CI, ammonia): *m/z* (%) = 649/647 (9/9) [M^+ + 2 H], 647/645 (1/1) [M^+], 632/630 (100/95) [M^+ - CH_3]; Anal. calcd. for $C_{36}H_{40}BrNO_5$ (646.6): C, 66.87; H, 6.23; N, 2.17. Found: C, 66.63; H, 6.17; N, 2.12.

(1*R*,3*R*,4b*M*,4b*P*)-[1,2-d]-8-Isopropoxy-9-methoxy-naphtho-[5,6-b]-*N*-benzyl-14-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolino-11H-pyran-11-one (19a/b). To a solution of **18** (800 mg, 1.24 mmol) in dry DMA (150 ml), dry NaOAc (750 mg, 7.50 mmol) and $(PPh_3)_2PdCl_2$ (175 mg, 250 µmol) were added and the mixture was stirred at 100 °C. The solvent was removed *in vacuo* and after filtration of the catalyst, the residue was purified by flash chromatography on deactivated (5% NH_3) silica gel with CH_2Cl_2 / methanol (100:2) as the eluent, to afford the two interconverting atropo-diastereomers **19a** and **19b** (484 mg, 69%, ratio 2.5:1), which were not separated; mp 83 °C; IR (KBr): $\tilde{\nu}$ 2950, 2910, 1715, 1575; ^{1}H NMR (200 MHz,$CDCl_3$) major isomer: δ = 0.84 (d, *J* = 6.0, 3H, 3-CH_3), 1.22-1.41 [m, 12H, 2 CH(C*H*$_3$)$_2$], 1.49 (d, *J* = 6.0, 3H, 1-CH_3), 1.75 (m, 2H, 4-H), 2.95 (d, *J* = 14.3, 1H, NC*H*HPh), 4.06 (s, 3H, OCH_3), 4.67 [q, *J* = 6.1, 2H, 2 C*H*(CH$_3$)$_2$], 6.87 (s, 1H, 7-H), 7.30-7.82 (m, 9H, Ar-H); minor isomer: δ = 0.84 (d, *J* = 6.0, 3H, 3-CH_3), 1.22-1.41 [m, 12H, 2 CH(C*H*$_3$)$_2$], 1.49 (d, *J* = 6.0, 3H, 1-CH_3), 1.75 (m, 2H, 4-H), 2.95 (d, *J* = 14.3, 1H, NC*H*HPh), 4.08 (s, 3H, OCH_3), 4.67 [q, *J* = 6.1, 2H, 2 C*H*(CH$_3$)$_2$], 6.87 (s, 1H, 7-H), 7.30-7.82 (m, 9H, Ar-H); MS (CI, isobutane): *m/z* (%) = 567 (5) [M^+ + 2 H], 566 (14) [M^+ + H], 565 (3) [M^+], 551 (38) [M^+ - CH_3 + H], 550 (100) [M^+ - CH_3]; Anal. calcd. for $C_{36}H_{39}NO_5 \times 1.5\ H_2O$ (592.7): C, 72.95; H, 7.14; N, 2.36. Found: C, 72.68; H, 7.31; N, 2.20.

(1*R*,3*R*,5*P*)- and (1*R*,3*R*,5*M*)-(2'-Hydroxymethyl-5'-isopropoxy-4'-methoxy-1'-(*N*-benzyl-6-hydroxy-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-naphthalene (20a) and (20b). A solution of **19a/19b** (200 mg, 354 µmol) in dry THF (50 ml) was treated with $LiAlH_4$ (38.0 mg, 1.00 mmol). After 5 min, hydrochloric acid (10 ml, 2 N) was added and the aqueous laver was extracted several times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was converted into the free base and chromatographed on deactivated (2.5% NH_3) silica gel with CH_2Cl_2 / methanol (100:5) as the eluent, to yield **20a** (117 mg, 205 µmol) and **20b** (46.0 mg, 80.9 µmol) as colorless crystals (methanol) each; **20a**: mp 174-176 °C; $[\alpha]_D^{20}$ = +80.4 (*c* = 0.69 in $CHCl_3$); CD (ethanol): $\Delta\varepsilon_{226}$ +210, $\Delta\varepsilon_{241}$ -24.3, $\Delta\varepsilon_{278}$ -10.8, $\Delta\varepsilon_{307}$ -0.36, $\Delta\varepsilon_{332}$ -7.67; IR (KBr): $\tilde{\nu}$ 3380, 2950, 2920, 1575, 1255; ^{1}H NMR (200 MHz, MeOH-d_4): δ = 1.01 (d, *J* = 6.6, 3H, 3-CH_3), 1.28 (d, *J* = 6.6, 3H, 1-CH_3), 1.32-1.49 [m, 12H, 2 CH(C*H*$_3$)$_2$], 1.77 (dd, *J* = 17.3, 4.9, 1H, 4-H_{eq}), 1.92 (dd, *J* = 17.3, 10.5, 1H, 4-H_{ax}), 3.24 (d, *J* = 13.8, 1H, NC*H*HPh), 3.31 (m_c, 1H, 3-H), 3.72 (d, *J* =13.8, 1H, NCH*H*Ph), 3.98 (q, *J* = 6.6, 1H, 1-H), 4.03 (s, 3H, OCH_3), 4.48-4.62 [m, 4H, 2 C*H*(CH$_3$)$_2$ and C*H*$_2$OH], 6.49 (s, 1H, 7-H), 6.95 (d, *J* = 8.4, 1H, 6'-H or 8'-H), 7.04 (d, *J* = 8.4, 1H, 6'-H or 8'-H), 7.12 (s, 1H, 3'-H), 7.2-7.4 (m, 6H, Ar-H); MS: *m/z* (%) = 569 (0.5) [M^+], 554 (87) [M^+ - CH_3]; Anal. calcd. for $C_{36}H_{43}NO_5 \times H_2O$ (595.3): C, 72.46; H, 7.77; N, 2.35. Found: C, 72.43;

H, 7.56; N, 2.18. **20b**: mp 106-108°C; $[\alpha]_D^{20}$ = +63.1 (*c* = 0.48 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3380, 2960, 2920, 1590, 1250; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.6, 3 H, 3-CH_3), 1.24 (d, *J* = 6.6, 3 H, 1-CH_3), 1.34-1.46 (m, 12 H, 2 CH(CH_3)$_2$), 1.88 (m, 2 H, 4-H), 3.25 (d, *J* = 14.1, 1 H, NC*H*HPh), 3.37 (m_c, 1 H, 3-H), 3.69 (d, *J* =13.8, 1 H, NCH*H*Ph), 3.97 (q, *J* = 6.6, 1 H, 1-H), 4.02 (s, 3 H, OCH_3), 4.48 (d, 2 H, CH_2OH), 4.56 (m, 2 H, 2 C*H*(CH_3)$_2$), 6.50 (s, 1 H, 7-H), 6.92 (d, *J* = 8.4, 1 H, 6'-H or 8'-H), 6.98 (d, *J* = 8.4, 1 H, 6'-H or 8'-H), 7.10 (s, 1 H, 3'-H), 7.2-7.4 (m, 6 H, Ar-H); MS (CI, isobutane): *m/z* (%) = 571 (40) [M^+ + 2 H], 570 (100) [M^+ + 1 H], 569 (5) [M^+], 554 (25) [M^+ - CH_3]; Anal. calcd. for $C_{36}H_{43}NO_5 \times H_2O$ (595.3): C, 72.46; H, 7.77; N, 2.35. Found: C, 72.60; H, 8.04; N, 2.16.

(1*R*,3*R*,5*M*)-5-(5'-Isopropoxy-4'-methoxy-2'-methyl-1'-naphthyl)-*N*-benzyl-6-hydroxy-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (21). To a solution of **20a** (84.7 mg, 149 μmol) in dry CH_2Cl_2 (15 ml), triphenylphosphane (78.6 mg, 30.0 μmol) and 1,2-dibromotetrachloroethane (98.1 mg, 30.0 μmol) were added subsequently and the mixture was stirred for 10 min. After removal of the solvent under reduced pressure, the residue was dissolved in dry THF (15 ml), cooled (0 °C) and $LiAlH_4$ (38.0 mg, 1.00 mmol) was added. The mixture was stirred for 10 min and treated with hydrochlorid acid (10 ml, 2 N). Exhaustive extraction of the aqueous laver with CH_2Cl_2, drying ($MgSO_4$) and evaporation of the solvent *in vacuo* gave a crude product, which was converted into the free base. Column chromatography on silica gel with CH_2Cl_2 / methanol (100:5) afforded **21** (78.1 mg, 95%) as a solid; mp 169-171 °C; $[\alpha]_D^{20}$ = +111.5 (*c* = 0.52 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3150, 2960, 2920, 1580, 1115; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.0, 3H, 3-CH_3), 1.34 (d, *J* = 6.0, 3H, 1-CH_3), 1.46 [d, *J* = 6.2, 12H, 2 CH(CH_3)$_2$], 1.8-2.0 (m, 2H, 4-H), 2.17 (s, 3H, 2'-CH_3), 3.23 (d, *J* = 13.8, 1H, NC*H*HPh), 3.38 (m_c, 1H, 3-H), 3.82 (d, *J* =13.8, 1H, NCH*H*Ph), 4.00 (s, 3H, OCH_3), 4.01 (m, 1H, 1-H), 4.53 [m, 2H, 2 C*H*(CH_3)$_2$], 6.49 (s, 1H, 7-H), 6.82 (s, 1H, 3'-H), 6.90 (d, *J* = 8.4, 1H, 6'-H or 8'-H), 6.99 (d, *J* = 8.4, 1H, 6'-H or 8'-H), 7.2-7.4 (m, 6H, Ar-H); MS (CI, isobutane): *m/z* (%) = 555 (39) [M^+ + 2 H], 554 (100) [M^+ + H], 553 (1) [M^+], 538 (27) [M^+ - CH_3]; Anal. calcd. for $C_{36}H_{43}NO_4 \times H_2O$ (571.8): C, 75.35; H, 8.11; N, 3.14. Found: C, 75.63; H, 7.93; N, 2.50.

***N*-Benzyl-8,5'-di-*O*-isopropyldioncophylline C (22).** A solution of **21** (48.4 mg, 90.0 μmol) and thallium ethanolate[2] in dry CH_2Cl_2 (10 ml) was stirred for 30 min at room temperature and then treated with trifluorsulfonic anhydride (37 μl, 225 μmol). After additional stirring for 5 min, the pH value was adjusted to *ca.* 8 with NH_3 (concd). The solvent was removed under reduced pressure and the residue was purified by column chromatography on deactivated (2.5% NH_3) silica gel with CH_2Cl_2 / methanol (100:2), to yield a crude product. This was dissolved in dry DMF (15 ml) and subsequently treated with ditriphenylphosphinopropane (dppp) (16.5 mg, 40.0 μmol), $(PPh_3)_2PdCl_2$ (14.0 mg, 20.1 μmol), dry tri-*n*-butylamine (119 μl, 49.9 μmol) and formic acid (30 μl). The mixture was heated at 100 °C for 2.5 h and the solvent was evaporated *in vacuo*.

The residue was dissolved in CH_2Cl_2 (20 ml) and washed with hydrochloric acid (5 ml, 2 N). After conversion into the free base, the crude product was chromatographed on deactivated (2.5% NH_3) silica gel with CH_2Cl_2 / methanol (100:2) as the eluent, to give **22** (33.0 mg, 68%) as an amorphous solid; mp 152-154 °C; $[\alpha]_D^{20}$ = +53.2 (*c* = 0.62 in $CHCl_3$); CD (ethanol): $\Delta\varepsilon_{205}$ -242, $\Delta\varepsilon_{227}$ +401, $\Delta\varepsilon_{257}$ -43.6, $\Delta\varepsilon_{280}$ -2.49, $\Delta\varepsilon_{296}$ -45.3, $\Delta\varepsilon_{303}$ -23.9, $\Delta\varepsilon_{313}$ -33.5; IR (KBr): $\tilde{\nu}$ 2960, 2920, 1590, 1245; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.0, 3H, 3-CH_3), 1.34 (d, *J* = 6.0, 3H, 1-CH_3), 1.43 [d, *J* = 6.2, 12H, 2 CH(CH_3)$_2$], 1.88-2.14 (m, 2H, 4-H), 2.12 (s, 3H, CH_3 an C-2'), 3.23 (d, *J* = 14.8, 1H, NC*H*HPh), 3.39 (m_c, 1H, 3-H), 3.78 (d, *J* =13.8, 1H, NCH*H*Ph), 3.99 (s, 3H, OCH_3), 4.06 (q, *J* = 6.0, 1H, 1-H), 4.56 [sept, *J* = 6.0, 2H, 2 C*H*(CH_3)$_2$], 6.78 (s, 1H, 3'-H), 6.80-7.00 (m, 4H, 6-H, 7-H, 6'-H and 8'-H), 7.19 (t, *J* = 7.6, 1H, 7'-H), 7.28-7.49 (m, 5H, Ar-H); MS: *m/z* (%) =537 (4) [M^+], 522 (99) [M^+ - CH_3], 480 (12) [M^+ - CH_3 - C_3H_7 + H]; Anal. calcd. for $C_{36}H_{43}NO_3$ (537.7): C, 80.41; H, 8.06; N, 2.60. Found: C, 80.59; H, 8.30; N, 2.43.

Dioncophylline C (1). To a cooled (-40 °C) solution of **22** (18.0 mg, 33.5 μmol) in dry CH_2Cl_2 (20 ml) boron trichloride (201 μl, 201 μmol, 1 M in hexane) was added and the the reaction mixture was allowed to warm up (-15 °C) for 5 h. After addition of methanol (5 ml), insoluble materials were filtered off and the solvent was removed under reduced pressure. The residue was converted into the free base and hydrogenated in methanol in the presence of Pd/C (10%) at normal pressure. After filtration of the catalyst, chromatography of the crude product on deactivated (5% NH_3) silica gel with CH_2Cl_2 / methanol (100:5) yielded **1** (11.4 mg, 94%) as a beige amorphous powder; mp dec. 248 °C (ref.[2] dec. 246 °C); $[\alpha]_D^{20}$ = +16.0 (*c* = 0.37 in $CHCl_3$) [ref.[2] +19.2 (c = 0.52 in $CHCl_3$)]; ^{13}C NMR (150 MHz, MeOH-d_4): δ = 20.5 (1-CH_3), 20.7 (2'-CH_3), 22.0 (3-CH_3), 35.9 (C-4), 43.0 (C-3), 48.6 (C-1), 56.7 (OCH_3), 107.9 (C-3'), 110.3 (C-6'), 113.6 (C-7), 114.8, 117.7 (C-8'), 127.6, 128.6 (C-7'), 129.9 (C-6), 131.3, 131.8, 135.0, 135.6, 137.6, 154.4 (C-8), 155.8 (C-4' or C-5'), 156.5 (C-5' or C-4'). CD, IR, ^{1}H, and mass spectral data were fully identical with those of an authentic sample previously obtained from *Triphyophyllum peltatum*.[2]

***N*-Formyldioncophylline C (23).** A mixture of **1** (75.4 mg, 207 μmol) and pivalic formic anhydride[26] (40 μl, 231 μmol) in dry CH_2Cl_2 (10 ml) was stirred at room temperature for 2 h. Removal of the solvent *in vacuo* afforded a yellow solid, which gave colorless crystals (**23**) from CH_2Cl_2 / petroleum ether (79.3 mg, 98%); mp 158-159 °C; $[\alpha]_D^{20}$ = +68.8 (*c* = 0.70 in $CHCl_3$); [lit.:[2] 68.3° (*c* = 0.70 in $CHCl_3$)]. **23** was identical in all spectroscopical data with a sample of *N*-formyldioncophylline C, as prepared previously.[2]

8-*O*-Acetyl-*N*-formyldioncophylline C (24). To a solution of **23** (56.2 mg, 144 μmol) in dry CH_2Cl_2 (10 ml) acetyl chloride (13 μl, 182 μmol), Et_3N (24 μl, 182 μmol) and a catalytic amount of *N,N*-dimethylamino-pyridine (DMAP) were added and the reaction mixture was stirred for 2 h. After treatment with an aqueous 2 N

NH_4Cl solution (5 ml) the organic laver was filtered over deactivated (5% NH_3) silica gel. Recrystallization from CH_2Cl_2 afforded **24** (60.6 mg, 97%) as a colorless microcrystalline solid; mp 201 °C; $[\alpha]_D^{20}$ = +83.9 (*c* = 0.50 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3395, 2920, 2906, 2818, 1752, 1650, 1594, 1382, 1192, 748; ^1H NMR (400 MHz, $CDCl_3$); main rotational isomer with respect to the *N*-formyl bond: δ = 1.11 (d, *J* = 6.5, 3H, 3-CH_3), 1.45 (d, *J* = 6.8, 3H, 1-CH_3), 2.10 (s, 3H, 2'-CH_3), 2.15 (dd, *J* = 16.0, 6.2, 1H, 4-H_{ax}), 2.41 (s, 3H, OAc), 2.59 (dd, *J* = 15.4, 4.1, 1H, 4-H_{eq}), 3.91 (m_c, 1H, 3-H), 4.11 (s, 3H, OCH_3), 5.54 (q, *J* = 6.3, 1H, 1-H), 6.62 (dd, *J* = 8.4, 1.0, 1H, 6'-H or 8'-H), 6.72 (s, 1H, 3'-H), 6.84 (dd, *J* = 7.6, 0.9, 1H, 8'-H or 6'-H), 7.07 (d, *J* = 8.4, 1H, 6-H or 7-H), 7.14 (d, *J* = 8.0, 1H, 7-H or 6-H), 7.22 (dd, *J* = 8.2, 7.8, 1H, 7'-H), 8.25 (s, 1H, CHO), 9.41 (s, 1H, OH); MS: *m/z* (%) = 433 (71) [M^+], 418 (9) [M^+ - CH_3], 391 (35) [M^+ - C_2H_2O], 376 (100) [M^+ - C_3H_5O]; Exact mass calcd. for $C_{26}H_{27}NO_5$ (M^+) 433.1889. Found: 433.1895.

8,8'''-Di-*O*-acetyl-*N,N'*-diformyl-5',5''-di-*O*-dehydro-jozimine C (25). A mixture of **24** (58.2 mg, 134 μmol), Et_3N (0.2%), and Ag_2O (331 mg, 1.43 mmol) in dry $CHCl_3$ (5 ml) was stirred for 39 h at 4 °C in the dark. After removal of the solvent, the residue was purified by column chromatography on deactivated (5% NH_3) silica gel with CH_2Cl_2 / methanol (100:5), to yield **25** (23.1 mg, 40%) as a deep-violet amorphous solid; mp dec. >230 °C; IR (KBr): $\tilde{\nu}$ 2950, 2926, 2855, 1735, 1662, 1605, 1390, 1200, 1120, 762; ^1H NMR (600 MHz, MeOH-d_4); main rotational isomer with respect of the *N*-formyl bond: δ = 1.09 (d, *J* = 6.4, 6H, 3-CH_3 and 3'''-CH_3), 1.41 (d, *J* = 6.4, 6H, 1-CH_3 and 1'''-CH_3), 2.15 (s, 6 H, 2'-CH_3 and 2''-CH_3), 2.23 (dd, *J* = 16.1, *J* = 4.8, 2H, 4-H_{ax} and 4'''-H_{ax}), 2.40 (s, 6H, 8-OAc and 8'''-OAc), 2.69 (dd, *J* = 15.7, 4.4, 2H, 4-H_{eq} and 4'''-H_{eq}), 4.00 (m_c, 2H, 3-H and 3'''-H), 4.11 (s, 6H, 4'-OCH_3 and 4''-OCH_3), 5.42 (q, *J* = 6.8, 2H, 1-H and 1'''-H), 6.59 (d, *J* = 8.9, 2H, 8'-H and 8''-H), 6.93 (s, 2H, 3'-H and 3''-H), 7.12 (d, *J* = 8.0, 2H, 6-H and 6'''-H or 7-H and 7'''-H), 7.17 (d, *J* = 8.5, 2H, 7-H and 7'''-H or 6-H and 6'''-H), 7.25 (d, *J* = 8.9, 2H, 7'-H and 7''-H), 8.22 (s, 2H, *N*-CHO and *N'*-CHO); MS: *m/z* (%) = 864 (2) [M^+ + 2], 836 (1) [M^+ + 2 - CO], 822 (3) [M^+ + 2 - C_2H_2O], 794 (1) [M^+ + 2 - $C_3H_2O_2$], 780 (1) [M^+ + 2 - $C_4H_4O_2$], 751 (1) [M^+ + 2 - $C_5H_5O_3$], 42 (100) [$C_2H_2O^+$]; Exact mass calcd. for $C_{52}H_{54}N_2O_{10}$ (M^+) 864.3622. Found: 864.3630.

Jozimine C (4). A cooled (0 °C) solution of **25** (14.8 mg, 17.1 μmol) in methanol (20 ml) was irradiated (Osram Power Star HQI/D discharge lamp, visible light) for 15 min and the solvent was evaporated *in vacuo*. A solution of the resulting oil in dry methanol (5 ml) was treated with 1 ml portions of cold satd. methanolic hydrochloric acid over a period of 24 h while gently refluxing. The solvent was removed under reduced pressure and HPLC of the residue on a semipreparative amino-bonded phase column (Rainin Dynamax-60A) with CH_2Cl_2 / methanol / $(NH_4)_2CO_3$ (90:10:0.1) afforded **4** (8.31 mg, 67%) as a colorless microcrystalline solid; mp dec. >236 °C; $[\alpha]_D^{20}$ = +21.5 (*c* = 0.05 in ethanol); CD (ethanol): $\Delta\varepsilon_{204}$ -45.5, $\Delta\varepsilon_{234}$ +25.1, $\Delta\varepsilon_{306}$ -12.3; IR (KBr): $\tilde{\nu}$ 3377, 2940, 2905, 2833, 1593, 1381, 1111, 751; ^1H NMR (600 MHz, MeOH-d_4): δ = 1.28

(d, J = 6.6, 6H, 3-CH_3 and 3'''-CH_3), 1.79 (d, J = 7.1, 6H, 1-CH_3 and 1'''-CH_3), 2.14 (s, 6H, 2'-CH_3 and 2''-CH_3), 2.31 (dd, J = 18.1, 11.4, 2H, 4-H_{ax} and 4'''-H_{ax}), 2.45 (dd, J = 17.8, 4.7, 2H, 4-H_{eq} and 4'''-H_{eq}), 3.70 (m_c, 2H, 3-H and 3'''-H), 4.12 (s, 6H, 4'-OCH_3 and 4''-OCH_3), 4.87 (q, J = 7.1, 2H, 1-H and 1'''-H), 6.68 (d, J = 8.8, 2H, 8'-H and 8''-H), 6.90 (d, J = 8.3, 1H, 7-H and 7'''-H), 6.94 (s, 2H, 3'-H and 3''-H), 6.94 (d, J = 8.2, 2H, 6-H and 6'''-H), 7.26 (d, J = 8.2, 2H, 7'-H and 7''-H); ^{13}C NMR (150 MHz, MeOH-d_4): δ = 18.1 (1-CH_3 and 1'''-CH_3), 19.2 (3-CH_3 and 3'''-CH_3), 20.6 (2'-CH_3 and 2''-CH_3), 33.1 (C-4 and C-4'''), 45.1 (C-3 and C-3'''), 49.7 (C-1 and C-1'''), 56.9 (4'-OCH_3 and 4''-OCH_3), 108.2 (C-3' and C-3''), 114.7 (C-7' and C-7''), 115.0, 116.6 (C-8 and C-8'''), 120.9, 121.9, 130.6, 131.4, 132.0, 132.1 (C-6 and C-6'''), 132.4 (C-7' and C-7''), 135.8, 136.6, 152.7 (C-8 and C-8''' or C-4' and C-4'' or C-5' and C-5''), 154.6 (C-4' and C-4'' or C-5' and C-5'' or C-8 and C- 8'''), 157.2 (C-5' and C-5'' or C-8 and C-8''' or C-4' and C-4''); MS (DCI, ammonia): m/z (%) = 726 (6) [M^+ + 2], 725 (10) [M^+ + 1], 133 (100); Anal. calcd. for $C_{46}H_{48}N_2O_6 \times CH_3OH$ (756.94): C, 74.58; H, 6.92; N, 3.70. Found: C, 74.50; H, 7.08; N, 3.64.

Biological Experiments. The antiprotozoal activity was measured *in vitro* as described before,[5] using asexual erythrocytic stages of *P. falciparum* (strain NF 54, clone A1A9). The inhibition of incorporation of radiolabelled hypoxanthine by the test compounds was considered as a measure for their parasite growth inhibiting capacities. The sigmoid dose response curve was linearized by probit analysis and the final results were expressed as IC_{50} values (µg/ml). The antiviral activity (HIV-1) was determined *in vitro* as published earlier,[27] using CEM-SS cells and an RF-strain of HIV-1. The results were expressed as EC_{50}-values, cytotoxicities as IC_{50}'s (both µg/ml).

ACKNOWLEDGEMENTS

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 251 "Ökologie, Physiologie und Biochemie pflanzlicher und tierischer Leistung unter Streß" and SFB 347 "Selektive Reaktionen Metall-aktivierter Moleküle", the UNDP / WORLD BANK / WHO Special Programme for Research and Training in Tropical Diseases (TDR), and the Fonds der Chemischen Industrie. J.H. thanks the Hermann-Schlosser-Stiftung for generous support. Furthermore, experimental help by Wael Saeb and technical assistance by Manuela Schäffer is gratefully acknowledged.

REFERENCES AND NOTES

1. "Acetogenic Isoquinoline Alkaloids", part 105; for part 104, see Bringmann, G.; Holenz, J.; Aké Assi, L.; Hostettmann, K. *Planta Med.*, submitted. - "Antiprotozoal Activity of Naphthylisoquinoline Alkaloids", part 10; for part 9, see ref. 6. - "HIV-Inhibitory Natural Products", part 44; for part 43, see Bokesch, H.; Young, S. M.; McKee, T. C.; Blunt, J. W.; Boyd, M. R. *Nat. Prod. Lett.*, in press.
2. Bringmann, G.; Rübenacker, M.; Weirich, R.; Aké Assi, L. *Phytochemistry* **1992**, *31*, 4019-4024.
3. Bringmann, G.; Pokorny, F. in *The Alkaloids*; Cordell, G. ed.; Academic Press: New York, Vol. 46, 1995, pp. 127-271.
4. François, G.; Timperman, G.; Holenz, J.; Aké Assi, L.; Geuder, T.; Maes, L.; Dubois, J.; Hanocq, M.; Bringmann, G. *Ann. Trop. Med. Parasitol.* **1996**, *90*, 115-123.
5. François, G.; Bringmann, G.; Dochez, C.; Schneider, C.; Timperman, G.; Aké Assi, L. *J. Ethnopharmacol.* **1995**, *46*, 115-120.
6. François, G.; Timperman, G.; Aké Assi, L.; Eling, W.; Holenz, J.; Bringmann, G. *Antimicrob. Agents Chemother.*, in press.
7. Bringmann, G.; Saeb, W.; Koppler, D.; François, G. *Tetrahedron* **1996**, *52*, 13409-13418.
8. Bringmann, G.; Rübenacker, M.; Jansen, J. R.; Scheutzow, D.; Aké Assi, L. *Tetrahedron Lett.* **1990**, *31*, 639-642.
9. Bringmann, G.; Jansen, J. R.; Reuscher, H.; Rübenacker, M.; Peters, K.; von Schnering, H. G. *Tetrahedron Lett.* **1990**, *31*, 643-642.
10. Bringmann, G. *Bull. Soc. Chim. Belg.* **1996**, *105*, 601-603.
11. Bringmann, G.; Götz, R.; François, G. *Tetrahedron* **1996**, *52*, 13419-13426.
12. Boyd, M. R.; Hallock, Y. F.; Cardellina II, J. H.; Manfredi, K. P.; Blunt, J. W.; McMahon J. B.; Buckheit Jr., R. W.; Bringmann, G.; Schäffer, M.; Cragg, G. M.; Thomas, D. W.; Jato, J. G. *J. Med. Chem.* **1994**, *37*, 1740-1745.
13. Hallock, Y. H.; Manfredi, K. P.; Blunt, J. W.; Cardellina II, J. H.; Schäffer, M.; Gulden, K.-P.; Bringmann, G.; Lee, A. Y.; Clardy, J.; François, G. *J. Org. Chem.* **1994**, *59*, 6349-6355.
14. Gable, R. W.; Martin, R. L.; Rizzacasa, M. A. *Aust. J. Chem.* **1995**, *48*, 2013-2021.
15. Bringmann, G.; Jansen, J. R.; Rink, H.-P. *Angew. Chem.* **1986**, *98*, 917-919; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 913-915.
16. Bringmann, G., Harmsen, S.; Schupp, O.; Walter, R. in Metal Assisted 'Twisting' of Axes: A Novel Approach to Stereoselective Biaryl Synthesis; Werner, H., Sundermeyer, J. eds.; Vieweg: Braunschweig, 1995, pp. 137-142.
17. Bringmann, G.; Götz, R. Harmsen, S.; Holenz, J.; Walter, R. *Liebigs Ann.* **1996**, 2045-2058.

18. Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kinzinger, L.; Ortmann, T. *Liebigs Ann. Chem.* **1993**, 877-888.
19. By the use of an *N*-trifluoroacetyl instead of the *N*-benzyl group, an atropo-diastereomeric ratio of >95:5 is obtained, similar to previous experience in the ancistrocladine synthesis.[3]
20. Bringmann, G.; Schneider, S. *Synthesis* **1983**, 139-141.
21. Despite its close structural similarity to korupensamines A (**2a**) and B (**2b**), the 'monomeric halves' of michellamine B, dioncophylline C (**1**) was not coupled by the highly substrate specific dimerization enzyme recently isolated from various *Ancistrocladus* species and even from *T. peltatum*: Schlauer, J., Wiesen, B., Rückert, M., Aké Assi, L., Haller, R. D., Bär, S., Fröhlich, K.-U., Bringmann, G. *Arch. Biochem. Biophys.*, in press.
22. Bringmann G.; Harmsen, S.; Holenz, J.; Geuder, T.; Götz, R.; Keller, P. A.; Walter, R. Hallock, Y. F.; Cardellina II, J. H.; Boyd, M. R. *Tetrahedron* **1994**, *50*, 9643-9648.
23. This is corroborated by spectroscopic hints at the presence of another regioisomeric product, although in small amounts.
24. Even by directed search, jozimine C (**4**) has not yet been found in dioncophylline C producing material of *T. peltatum*.
25. Tiecco, M. *Synthesis* **1988**, 749-592.
26. Vlietstra, E. J.; Zwikker, J. W.; Nolte, R. J. M.; Drenth, W. *J. R. Neth. Chem. Soc.* **1982**, *101*, 460-462.
27. Gulakowski, R. J.; McMahon, J. B.; Staley, P. G.; Moran, R. A.; Boyd, M. R. *J. Virol. Methods* **1991**, *33*, 87-100.