Natural Products

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Total Synthesis of the Biscarbazole Alkaloids Murrafoline A–D by a Domino Sonogashira Coupling/Claisen Rearrangement/ Electrocyclization Reaction**

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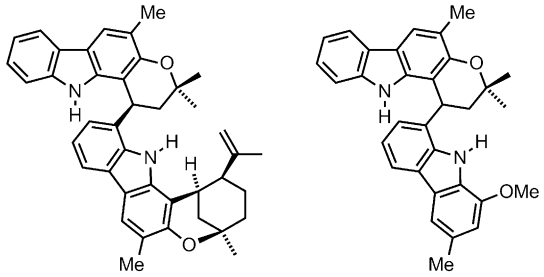
Carbazole alkaloids continue to attract strong interest because of their structural variety and promising pharmacological activities.[1] Besides their useful biological profile, biscarbazole alkaloids have synthetically challenging structures.[1,2] In 1983, Furukawa and co-workers described the isolation of murrafoline A (**1**) from the root bark of the Chinese medicinal plant *Murraya euchrestifolia* (Scheme 1).[3]

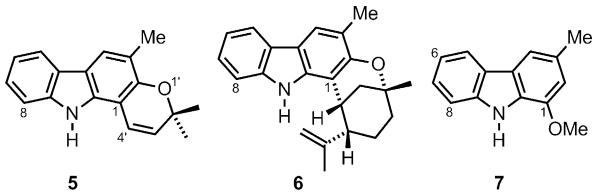


murrafoline A (**1**) murrafoline B (**2**)

murrafoline C (**3**) murrafoline D (**4**)

Scheme 1. Structures of the murrafolines A–D (**1**–**4**).

Murrafoline A (**1**) occurs in nature in racemic form. Its relative configuration was confirmed by X-ray crystal-structure analysis.[3] In the following decade, Furukawa and co-workers isolated further aryl–pyran-linked biscarbazole alkaloids from the same natural source: murrafoline B (**2**), C (**3**), and D (**4**), which were all obtained as racemates.[4,5] The characteristic structural feature of these alkaloids is a dihydrogirinimbine moiety (the structure of girinimbine (**5**) is shown in Scheme 2), which is attached at the C4′ atom of the



5 **6** **7**

Scheme 2. Structures of girinimbine (**5**), cyclomahanimbine (curryanin, murrayazolidine; **6**), and murrayafoline A (**7**).

pyran ring to a second carbazole framework. In the case of murrafoline A (**1**), the dihydrogirinimbine moiety is attached to C8 of the carbazole nucleus of cyclomahanimbine (**6**), in murrafoline B (**2**) and D (**4**) to C8 and C6, respectively, of the carbazole nucleus of murrayafoline A (**7**), and in murrafoline C (**3**) to C8 of the carbazole nucleus of girinimbine (**5**). All three monomeric carbazole units present in murrafolines A–D (**1**–**4**) have also been isolated from *M. euchrestifolia*: the pyrano[3,2-*a*]carbazole girinimbine (**5**), the cyclized monoterpenoid pyrano[3,2-*a*]carbazole cyclomahanimbine (**6**), and the 1-oxygenated tricyclic carbazole alkaloid murrayafoline A (**7**) (Scheme 2).[6]

By using organometallic chemistry for carbazole construction, we previously developed synthetic routes to girinimbine (**5**),[7,8] cyclomahanimbine (**6**),[8] and murrayafoline A (**7**).[9] A recent approach to girinimbine (**5**) relies on the 2-propargyloxycarbazole **10** as a crucial intermediate (Scheme 3).[8] On heating in toluene at reflux, a reaction sequence involving a Claisen rearrangement to **10a**, enolization and a 1,5-H shift to give **10b**, and finally electrocyclic ring closure led to **5**.[10]

Herein, we describe the first total synthesis of the murrafolines A–D by a novel domino reaction sequence. Domino reactions have proven to be ideal for efficiently generating high molecular complexity in one-pot processes because multistep transformations are executed without intermediate workup.[11] Therefore, we aimed to construct

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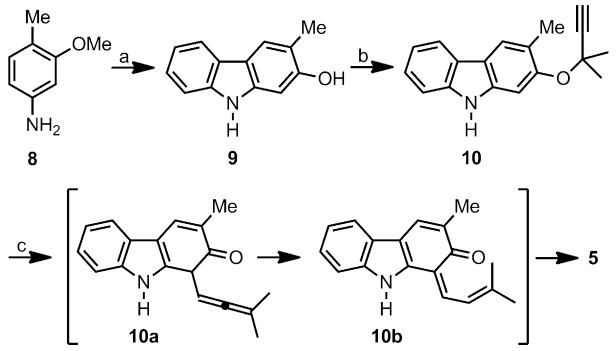
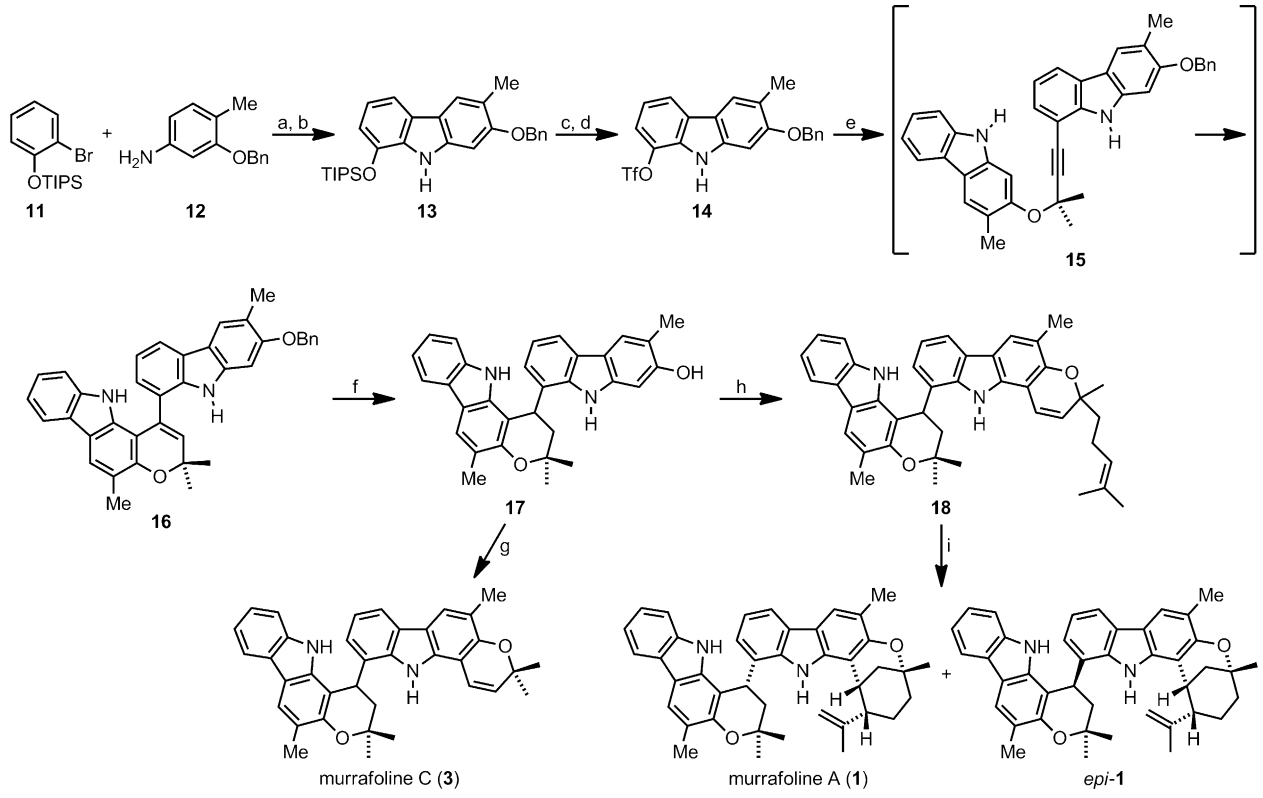


Scheme 3. Synthesis of girinimbine (**5**) via the 2-propargyloxycarbazole **10**: a) 1. PhI, $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), Cs_2CO_3, toluene, 100°C, 26 h; 2. $Pd(OAc)_2$ (5 mol%), K_2CO_3 (5 mol%), pivalic acid, air, 100°C, 24 h; 3. BBr_3, CH_2Cl_2, −78°C→RT, 15.5 h (85%); b) methyl 2-methylbut-3-yn-2-yl carbonate (1.5 equiv), Cs_2CO_3 (2 equiv), CuI (0.5 mol%), acetonitrile, RT, 24 h (65%); c) toluene, reflux, 29 h (55%). SPhos = 2-dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl.

the characteristic aryl–pyran linkage of the murrafolines at the stage of intermediate **10** by a palladium-catalyzed Sonogashira coupling to the terminal alkyne.[12] This process could then perhaps be combined in a one-pot reaction with the sequence of steps leading to annulation of the pyran ring (see Scheme 3) and thus directly provide the aryl–pyran-linked biscarbazole framework in a domino reaction.

Owing to their substitution pattern, we projected the synthesis of murrafoline A (**1**) and murrafoline C (**3**) by the same approach (Scheme 4). We assembled the carbazole framework by our palladium-catalyzed synthesis:[13,14] Buchwald–Hartwig coupling of the aryl bromide **11** and aniline **12** with DavePhos as the ligand,[15] followed by palladium(II)-catalyzed oxidative cyclization, afforded the desired 2,8-dioxygenated carbazole **13**, which was desilylated and converted into the carbazol-8-yl triflate **14**. Sonogashira coupling of **14** and the 2-propargyloxycarbazole **10** to give the aryl propargyl ether **15** was immediately followed by the sequence of Claisen rearrangement, enolization, 1,5-H shift, and electrocyclic ring closure to provide the biscarbazole **16**. This one-pot process was promoted by the addition of xylene and heating at reflux after completion of the Sonogashira coupling (see the Experimental Section). Hydrogenation of the double bond in the pyran ring occurred with concomitant cleavage of the benzyl ether to afford compound **17**. The formation of a dimethylpyran ring at the hydroxycarbazole unit of **17** by the Lewis acid promoted annulation of prenal[8,16] afforded murrafoline C (**3**).[17] Alternatively, a Lewis acid promoted reaction of **17** with citral provided compound **18**, which on proton-catalyzed cycloisomerization



Scheme 4. Synthesis of murrafoline A (**1**) and murrafoline C (**3**): a) **12** (1.5 equiv), $[Pd_2(dba)_3]$ (6 mol%), DavePhos (12 mol%), NaO*t*Bu (1.2 equiv), toluene, reflux, 24 h (98%); b) $Pd(OAc)_2$ (20 mol%), K_2CO_3 (20 mol%), pivalic acid, 85°C, 20 h (85%); c) TBAF (1.5 equiv), THF, 0°C→RT, 2 h (100%); d) Tf_2O (1.2 equiv), pyridine, 0°C→RT, 12 h (74%); e) 1. **10** (1.3 equiv), $[Pd(PPh_3)_4]$ (10 mol%), CuI (0.5 mol%), piperidine, RT, 20 h; 2. xylene, reflux, 1.5 h (61%); f) 30% Pd/C, H_2, EtOAc, RT, 2 d (97%); g) prenal (2 equiv), $Ti(OiPr)_4$ (4 equiv), −78°C→RT, 22 h (75%); h) citral (2 equiv), $Ti(OiPr)_4$ (4 equiv), −78°C→RT, 20 h (89%); i) camphorsulfonic acid (2 equiv), toluene, RT, 7 d (77%; **1**/*epi*-**1** 1:1). Bn = benzyl, DavePhos = 2-(dicyclohexylphosphanyl)-2′-(*N*,*N*-dimethylamino)biphenyl, dba = dibenzylideneacetone, TBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl.

led to murrafoline A (**1**) and its non-natural diastereoisomer *epi*-**1** (77% yield, 1:1 mixture). The two diastereoisomers were separated by HPLC[18] and fully characterized,[17] and the structure of the natural product was confirmed by X-ray crystallographic analysis (Figure 1).[19]

We then extended our methodology to the synthesis of murrafoline B (**2**; Scheme 5). The coupling of **11** with aniline **19** and subsequent oxidative cyclization led to the carbazole **20**, which after removal of the silyl group was converted into the triflate **21**. The treatment of **21** with the 2-propargyloxycarbazole **10** directly provided the biscarbazole **22** through the domino Sonogashira coupling/Claisen rearrangement/electrocyclization sequence. Reduction with lithium aluminum hydride followed by catalytic hydrogenation of the pyran double bond gave murrafoline B (**2**).[17]

For the synthesis of murrafoline D (**4**), we used mukonine (**23**) as the starting material (Scheme 6). Mukonine (**23**) can be prepared either by a previously reported iron-mediated or by the palladium-catalyzed carbazole synthesis.[20,21] By our improved route based on palladium catalysis, mukonine (**23**) was prepared in two steps and 91% overall yield.[21c] Electrophilic iodination of **23** afforded 6-iodomukonine (**24**), which underwent a domino reaction with the 2-propargyloxycarbazole **10** to afford the biscarbazole **25** in excellent yield (89%). The structure of **25** was confirmed by X-ray crystal-structure determination (Figure 2).[22] Reduction of the ester to

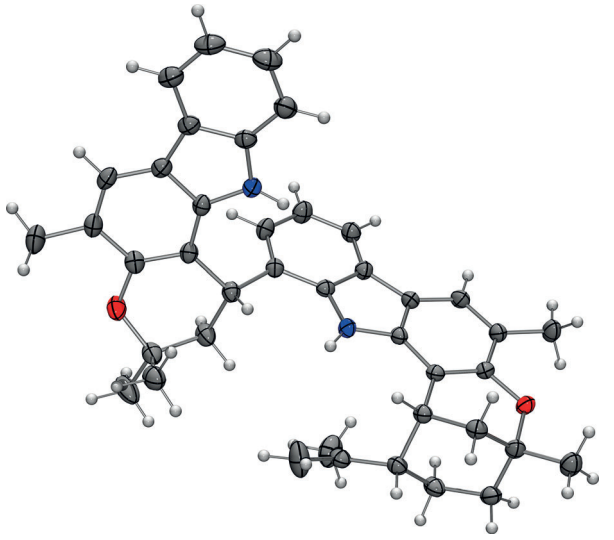
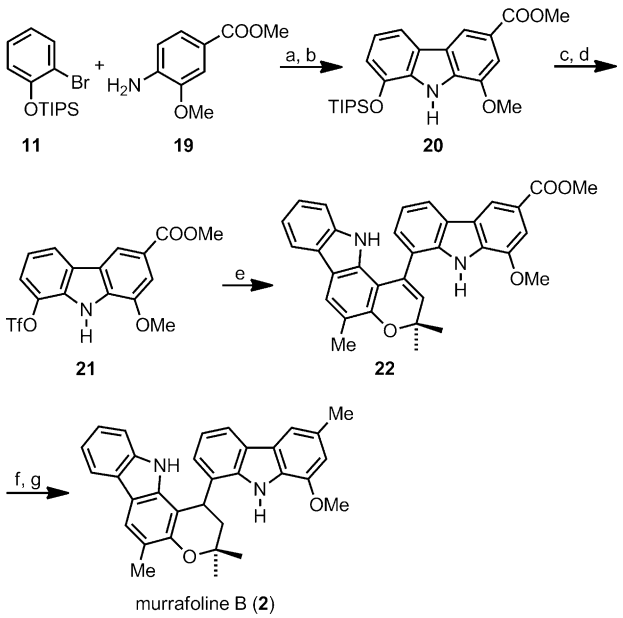
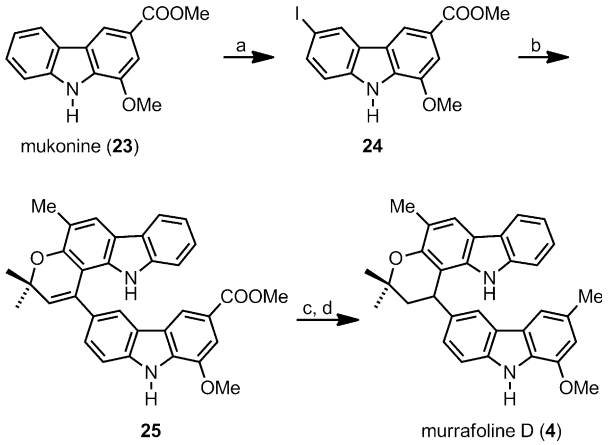


Figure 1. Molecular structure of murrafoline A (**1**) in the crystal (ORTEP plot showing thermal ellipsoids at the 50% probability level).



Scheme 5. Synthesis of murrafoline B (**2**): a) **11** (1.1 equiv), $[Pd_2(dba)_3]$ (6 mol%), SPhos (12 mol%), Cs_2CO_3 (1.4 equiv), toluene, reflux, 24 h (98%); b) $Pd(OAc)_2$ (1.1 equiv), AcOH, reflux, 24 h (67%); c) TBAF (1.5 equiv), THF, 0.5 h, 0°C→RT (100%); d) Tf_2O (1.2 equiv), pyridine, −15°C→RT, 2 h (90%); e) 1. **10** (1.3 equiv), $[Pd(PPh_3)_4]$ (10 mol%), CuI (0.5 mol%), piperidine, RT, 2 d; 2. xylene, reflux, 2 h (39%); f) $LiAlH_4$ (4 equiv), CH_2Cl_2/Et_2O (1:1), RT, 6 h (63%); g) 30% Pd/C, H_2, EtOAc, RT, 4 d (95%).



Scheme 6. Synthesis of murrafoline D (**4**): a) KI (1.4 equiv), KIO_3 (1.5 equiv), AcOH, 55°C, 3 h (100%); b) 1. **10** (1.3 equiv), $[Pd(PPh_3)_4]$ (10 mol%), CuI (0.5 mol%), piperidine, RT, 12 h; 2. xylene, reflux, 2 h (89%); c) $LiAlH_4$ (4 equiv), CH_2Cl_2/Et_2O (1:1), RT, 5 h (78%); d) 30% Pd/C, H_2, EtOAc, RT, 16 h (92%).

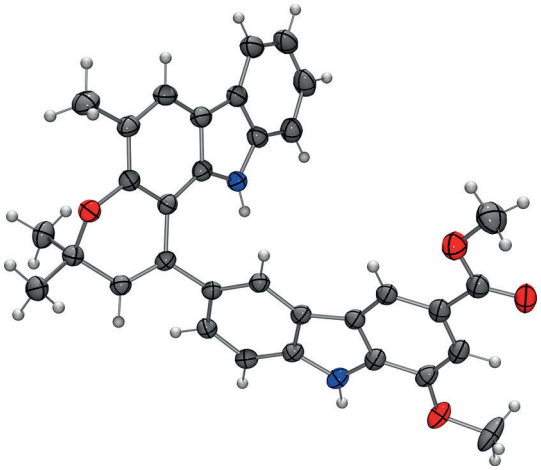


Figure 2. Molecular structure of the biscarbazole **25** in the crystal (ORTEP plot showing thermal ellipsoids at the 50% probability level).

a methyl group, followed by hydrogenation of the pyran ring, completed this total synthesis and provided murrafoline D (**4**) in four steps and 62% overall yield from mukonine (**23**).[17]

In conclusion, our present results emphasize that the reaction sequence of Sonogashira coupling, Claisen rearrangement, and electrocyclic ring closure, which can be performed as one-pot process, is ideal for the assembly of the framework of aryl–pyran-linked biscarbazole alkaloids of the murrafoline type. Thus, a domino reaction of the 2-propargyloxycarbazole **10** with the appropriately functionalized carbazolyl triflate **14** or **21** or iodocarbazole **24** provided direct routes to murrafolines A–D (**1**–**4**). Further elaboration of this synthetic approach and an investigation of the biological activity of the murrafolines are in progress.

Experimental Section

Synthesis of **16**: The 2-propargyloxycarbazole **10** (196 mg, 746 μmol), $[Pd(PPh_3)_4]$ (66 mg, 57.4 μmol), and CuI (0.54 mg, 2.8 μmol) were added to a solution of the carbazol-8-yl triflate **14** (250 mg, 574 μmol) in piperidine (5 mL), and the reaction mixture was stirred for 20 h at room temperature under an argon atmosphere. Xylene (10 mL) was then added, and the mixture was heated at reflux for 90 min, then poured into a saturated aqueous solution of NH_4Cl. The resulting mixture was extracted three times with CH_2Cl_2, the combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was evaporated. Purification of the crude product by flash chromatography on silica gel (EtOAc/pentane, 9:1) provided the biscarbazole **16** (192 mg, 61%) and **14** (35 mg, 14%). **16**: colorless crystals; m.p.: 158 °C; UV (MeOH): $\lambda = 217$ (sh), 238, 278 (sh), 288, 304 (sh), 337 (sh), 358 (sh) nm; fluorescence (MeOH): $\lambda_{ex} = 288$ nm, $\lambda_{em} = 361$ nm; IR (KBr): $\tilde{\nu} = 3443$, 2919, 2849, 2030, 1631, 1606, 1578, 1492, 1415, 1286, 1199, 1142, 1049, 1026, 817, 739, 692, 620 cm^{-1}; ^1H NMR (500 MHz, [D$_6$]acetone): $\delta = 1.55$ (m, 3H), 1.61 (m, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 5.11 (s, 2H), 5.97 (s, 1H), 6.85 (d, $J = 7.9$ Hz, 1H), 6.91 (s, 1H), 6.98–7.06 (m, 2H), 7.23–7.26 (m, 2H), 7.29 (br t, $J = 7.5$ Hz, 1H), 7.36 (br t, $J = 7.5$ Hz, 2H), 7.46 (d, $J = 7.1$ Hz, 2H), 7.64 (br s, 1H), 7.83 (s, 1H), 7.89 (d, $J = 7.2$ Hz, 1H), 7.92 (s, 1H), 8.12 (dd, $J = 6.8$, 2.4 Hz, 1H), 9.91 ppm (br s, 1H); ^{13}C NMR (125 MHz, [D$_6$]acetone): $\delta = 16.63$ (CH_3), 17.03 (CH_3), 27.21 (CH_3), 27.30 (CH_3), 70.35 (CH_2), 76.31 (C), 95.17 (CH), 106.42 (C), 111.31 (CH), 117.04 (C), 118.39 (C), 119.27 (C), 119.50 (CH), 119.63 (CH), 119.70 (C), 119.95 (CH), 120.05 (CH), 122.16 (CH), 122.37 (CH), 122.42 (C), 123.53 (C), 124.76 (C), 124.82 (CH), 124.93 (CH), 127.92 (2CH), 128.40 (CH), 129.22 (2CH), 130.78 (CH), 130.94 (C), 135.58 (C), 138.56 (C), 138.64 (C), 140.19 (C), 140.93 (C), 151.63 (C), 157.30 ppm (C); ESI-MS: m/z 549.3 $[M+H]^+$, 566.2 $[M+NH_4]^+$; elemental analysis: calcd (%) for $C_{38}H_{32}N_2O_2$: C 83.18, H 5.88, N 5.11; found: C 82.98, H 5.57, N 5.24.

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[17] Murrafoline A (**1**): colorless crystals; m.p.: 267 °C (lit.:[3,5] 260–262 °C); elemental analysis: calcd (%) for $C_{41}H_{42}N_2O_2$: C 82.79, H 7.12, N 4.71; found: C 82.40, H 7.97, N 4.32. *epi*-Murrafoline A (*epi*-**1**): colorless crystals; m.p.: 225 °C. Murrafoline B (**2**): colorless crystals; m.p.: 228 °C (lit.:[4,5] 234–237 °C); elemental analysis: calcd (%) for $C_{32}H_{30}N_2O_2$: C 80.98, H 6.37, N 5.90; found: C 81.00, H 6.74, N 5.70. Murrafoline C (**3**): colorless crystals, m.p.: 225 °C (lit.:[4,5] colorless oil); elemental analysis: calcd (%) for

$C_{36}H_{34}N_2O_2$: C 82.10, H 6.51, N 5.32; found: C 81.38, H 7.14, N 5.41. Murrafoline D (**4**): colorless crystals; m.p.: 274 °C (lit.:[5] amorphous powder, no m.p. given); elemental analysis: calcd (%) for $C_{32}H_{30}N_2O_2$: C 80.98, H 6.37, N 5.90; found: C 80.83, H 6.69, N 5.36. For the ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra of murrafolines A–D (**1**–**4**), see the Supporting Information.

[18] Chiral phase: Nucleocel δ-RP (Macherey–Nagel), column dimensions: 250 × 2.1 mm^2, temperature: 20 °C, eluent: MeCN/H_2O (85:15), flow rate: 12 mL min^{-1}.

[19] Crystallographic data for **1**: $C_{41}H_{42}N_2O_2$, $M = 594.77$ g mol^{-1}, crystal size: 0.43 × 0.26 × 0.25 mm^3, monoclinic, space group $P2_1/c$, $a = 11.880(1)$, $b = 12.416(1)$, $c = 21.633(2)$ Å, $\beta = 93.801(7)°$, $V = 3183.9(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.241$ g cm^{-3}, $\mu = 0.076$ mm^{-1}, $\lambda = 0.71073$ Å, $T = 198(2)$ K, θ range: 3.10–27.00°, reflections collected: 32306, independent: 6902 ($R_{int} = 0.0516$), 412 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0474$, $wR_2 = 0.1077$; maximal residual electron density: 0.199 e Å^{-3}. CCDC 948510 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[22] Crystallographic data for **25**: $C_{34}H_{32}Cl_2N_2O_5$, $M = 619.52$ g mol^{-1}, crystal size: 0.38 × 0.25 × 0.15 mm^3, monoclinic, space group $C2/c$, $a = 35.976(3)$, $b = 14.475(1)$, $c = 13.004(1)$ Å, $V = 6520.6(9)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.262$ g cm^{-3}, $\mu = 0.242$ mm^{-1}, $\lambda = 0.71073$ Å, $T = 198(2)$ K, θ range: 1.18–26.00°, reflections collected: 63047, independent: 6286 ($R_{int} = 0.0963$), 446 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0729$, $wR_2 = 0.02073$; maximal residual electron density: 0.765 e Å^{-3}. The crystal contains a void filled with disordered solvent molecules (1719 Å^3 per cell unit), which were modeled by dichloromethane and water molecules. CCDC 948511 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

