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Enantioselective Synthesis of (+)-Malbrancheamide B

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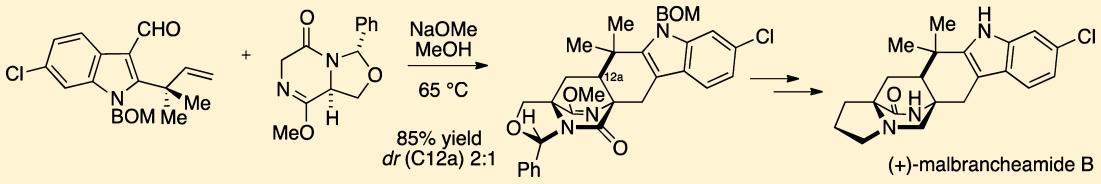
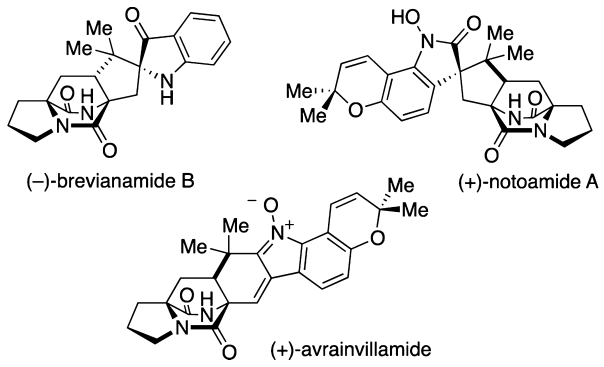
Supporting Information



ABSTRACT: The asymmetric total synthesis of the chlorinated [2.2.2]-diazabicyclic indole alkaloid (+)-malbrancheamide B is reported. Key to the synthesis is a domino reaction sequence that employs an aldol condensation, alkene isomerization, and intramolecular Diels–Alder cycloaddition. Diastereofacial selection between the azadiene stereofaces is enforced with a chiral aminal auxiliary. A formal 7-step (longest linear route) synthesis of (±)-malbrancheamide B is also reported.

INTRODUCTION

Prenylated indole alkaloids containing the [2.2.2]-diazabicyclic skeleton are the focus of vibrant research efforts across diverse scientific disciplines, from chemistry through biology and medicine. Beginning with the initial discovery of the brevianamides in 1969,[1] new metabolites continue to be revealed from *Aspergillus*, *Penicillium* and *Malbranchea* fungal species, and nearly 70 distinct metabolites are now known to share in common the [2.2.2]-diazabicyclic core.[2] Despite this shared skeletal feature, striking structural diversity is observed across the family. Variations in ring size and fusion, oxidation state, as well as the extent and location of methylation, halogenation, and prenylation are found between various congeners.[3] Stereochemical differences within the natural product family are also noted. Metabolites display both the *syn* and *anti* architecture[4] at the [2.2.2]-diazabicyclic core, and several natural products have been isolated from different sources in the opposite enantiomeric series (e.g., (+)- and (−)-notoamide A).[5] Brevianamide B, notoamide A, and avrainvillamide are illustrated as representative examples that highlight some of the structural diversity found within this natural product class.



The [2.2.2]-diazabicyclic core is believed to arise from a biogenic intramolecular hetero-Diels–Alder cycloaddition between a 5-hydroxypyrazine-2(1*H*)-one and the terminal alkene derived from reverse prenylation on the starting tryptophan module. This biosynthetic hypothesis was originally proposed by Porter and Sammes[6] in 1970 and has been extensively probed and supported over the decades by Williams and co-workers through a number of biomimetic total syntheses[7,8] and model studies.[9] In addition to the body of synthetic evidence, a number of isotopic precursor feeding experiments have in many cases discerned the order of bond formation and advanced informed biosynthetic pathways.[10] These natural products have also recently enjoyed investigation at the genomic and biochemical levels.[11] The biosynthetic gene clusters for four alkaloids have been cloned, and several biosynthetic enzymes have been expressed and characterized, although evidence for the intervention of a Diels–Alderase has not yet been fully established.

In addition to the impressive structural diversity and intriguing biosynthetic questions, many [2.2.2]-diazabicyclic alkaloids possess potent and diverse biological activities including antihelmintic, antitumor, and insecticidal properties.[12] Both the motivating bioactivities and intricate structure of these alkaloids have sustained the interest of synthetic chemists, and as a result, several methods for construction of the [2.2.2]-diazabicyclic core have been developed.[7,13] Improvements in the generality, efficiency, and selectivity of these synthetic methods are valuable objectives that stand to benefit the larger field and streamline investigation into the biological properties of these alkaloids as well as aid in the preparation of new bioactive molecules (and the understanding of structure–activity relationships). Our previous synthetic efforts in this area have focused on the development of diastereoselective hetero-DA reactions of diketopiperazine azadiene intermediates.[14,15] We selected as targets the

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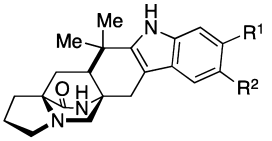
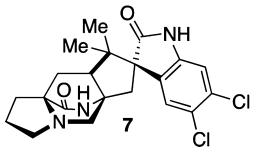
malbrancheamide group of [2.2.2]-diazabicyclic alkaloids on which to apply our asymmetric synthetic methods.

The malbrancheamides (**1**–**7**) are a group of metabolites within the larger [2.2.2]-diazabicyclic alkaloid family that feature halogenation at the indole nucleus. Malbrancheamide (**1**) and malbrancheamide B (**2**) were isolated from cultured *Malbrancheа aurantiaca* RRC1813, a fungal strain originally collected from bat guano found in a Mexican cave.[16] More recently, several new members have been isolated including the regioisomeric chlorinated derivate **4** and spiromalbramide (**7**) as well as the brominated derivatives **5** and **6**, which were produced from cultures grown on bromide-enriched media.[17]



(+)-malbrancheamide	(**1**)	R^1 = Cl, R^2 = Cl
(+)-malbrancheamide B	(**2**)	R^1 = Cl, R^2 = H
(+)-premalbrancheamide	(**3**)	R^1 = H, R^2 = H
(+)-isomalbrancheamide B	(**4**)	R^1 = H, R^2 = Cl
(+)-malbrancheamide C	(**5**)	R^1 = Br, R^2 = H
(+)-isomalbrancheamide C	(**6**)	R^1 = H, R^2 = Br



7 (–)-spiromalbramide

Although not all malbrancheamides have been extensively evaluated for biological activity, **1** and **2** are known to effect selective inhibition of calmodulin (CaM)-dependent phosphodiesterase (PDE1) activity.[16,18] PDE1 is a clinically validated[19] drug target, and selective inhibitors hold promising implications for the treatment of neurodegenerative[20] and vascular disease and cancer. Previous synthetic efforts on the malbrancheamides include a biomimetic IMDA approach by Williams and co-workers, which led to the synthesis of racemic **1**, **2**, and a number of C12a epimeric derivatives;[21] additionally, Simpkins and co-workers have disclosed their synthesis of *ent*-(–)-**2** using a cation-olefin cyclization strategy.[22]

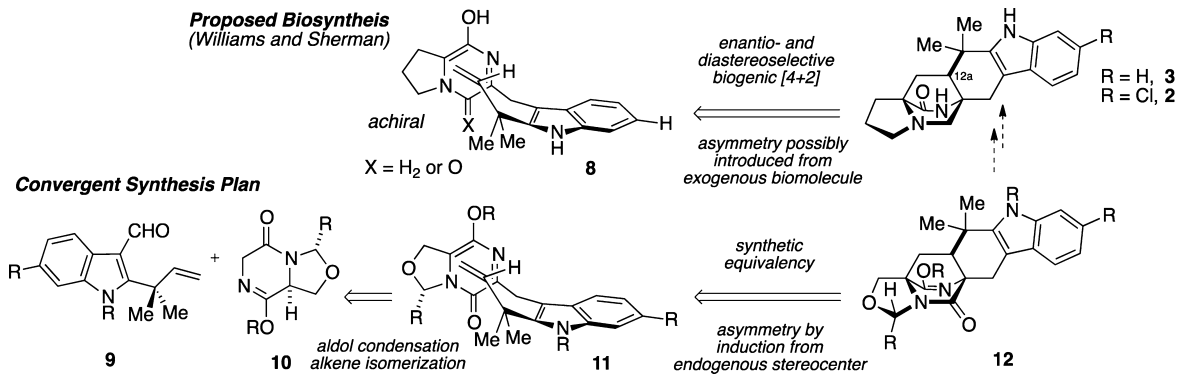
RESULTS AND DISCUSSION

As a result of studies by Williams, Sherman and co-workers, a number of aspects of malbrancheamide biosynthesis have been revealed, the sequence of biogenic bond construction is more clearly understood, and the key IMDA is postulated to occur on the intermediate resembling **8** (Scheme 1).[23] Because this intermediate is achiral, the ensuing cycloaddition in the absence of an intervening catalyst to discriminate between the azadiene stereofaces will result in racemic cycloadducts. Williams has validated this sequence in his biomimetic total synthesis.[21] Our synthetic strategy directed toward the malbrancheamide family of alkaloids also centers on the powerful IMDA strategy but employs a removable aminal auxiliary in order to achieve diastereofacial selection in the IMDA cycloaddition event (see intermediate **11**). We expected that the derived cycloadduct from our asymmetric synthetic route (**12**) could be converted to the target molecule in a short sequence. In this way, we anticipated that the first enantioselective synthesis of natural (+)-malbrancheamides could be achieved.

In addition to an asymmetric stereoselective synthesis, we strived to design for a general convergent assembly that could provide access to all members within the malbrancheamide group. Correspondingly, our retrosynthetic analysis led us toward a two-component approach, where the indole and chiral diketopiperazine (DKP) functions would be separated. In the forward direction, we anticipated that a domino[24] reaction sequence might be possible that brought about the union of indole **9** and DKP **10** through aldol condensation and, under the basic reaction conditions, would also permit alkene isomerization to the reactive azadiene, an intermediate that would subsequently react via cycloaddition and terminate the reaction sequence.

We directed our initial efforts toward the synthesis of malbrancheamide B (**2**) because the constitutionally associated 6-chloroindole starting material was commercial available. The desired indole carboxaldehyde **13** was prepared from 6-chloroindole in four steps. For this sequence of transformations leading to **13**, we were mostly able to follow precedented chemistry.[21] We prepared DKP **14** (3 steps, 1 chromatographic separation, 80% overall yield from proline methyl ester) as a simplified substrate that would permit evaluation of our proposed domino chemistry. On exposure to base (NaOMe in MeOH at 90 °C sealed tube), the mixture of the *N*-benzyloxymethyl (BOM) protected indole **13**[25] and DKP **14** afforded a mixture of three diazabicyclic cycloadducts **17a**–**c** in nearly quantitative combined yield (Scheme 2). This reaction sequence can be rationalized by initial enolization of DKP **14** followed by addition to the aldehyde in **13** to give the intermediate aldol condensation product **15**. Isomerization of the exocyclic alkene in **15** to the reactive endocyclic azadiene **16** is effected under the basic reaction conditions. IMDA cycloaddition of the azadiene terminates the reaction sequence and provides **17a** and **17b**. Diketopiperazine product **17c** arises from

Scheme 1. Proposed Biosynthesis and Our Synthesis Plan for the Malbrancheamides



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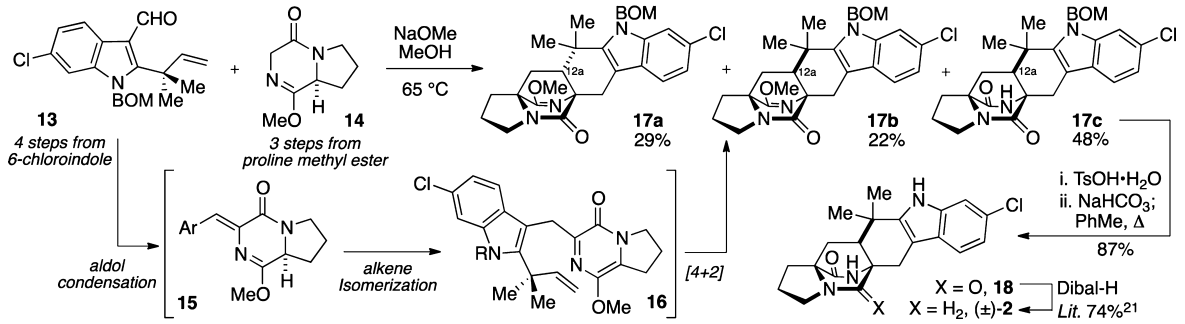
Scheme 2. Domino Reaction Sequence for the Synthesis of (±)-Malbrancheamide B



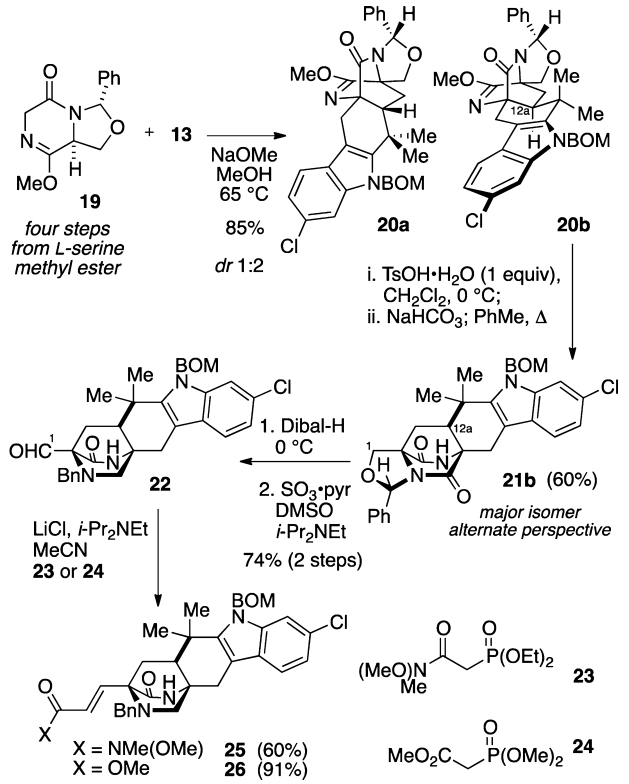
lactim hydrolysis of cycloadduct **17b** during the course of the reaction. Interestingly, hydrolysis is selective for *syn*-fused **17b**; no lactim ether hydrolysis product is observed for the more congested *anti*-configured diastereomer **17a**. Overall, *anti*-**17a** and the sum of *syn*-fused lactim ether **17b** and *syn*-diketopiperazine **17c** correspond to a diastereomer ratio (at C12a) of 1:2.3 as judged by the unpurified ^{1}H NMR. This "one pot" domino sequence effectively couples the two starting components and rapidly generates molecular complexity in excellent yield.

Because this simplified model intercepts the achiral IMDA precursor **16**, the resulting cycloadducts are produced as racemic mixtures. Both **17b** and **17c** can be easily converted to *oxo*-malbrancheamide B (**18**). Although we have employed several strategies to deprotect the lactim *O*-methyl ether and remove the BOM indole residue on **17b** and **17c**, because of operational simplicity and optimal results, we favor hydrolysis with TsOH·H_2O (2 equiv) in CH_2Cl_2 at room temperature. These mild conditions effect BOM (and imine cleavage on **17b**), producing an intermediate ammonium methyl ester (not shown).[26] On basification ($NaHCO_3$), the derived free amine condenses with the pendant ester to give lactam **18** and thereby re-establish the [2.2.2]-bridged architecture. In practice, the cyclization to lactam **18** was facilitated by heating in toluene. Overall, this process reliably afforded product **18** (87% yield from **17c**; 61% from **17b**), intercepting the penultimate precursor from Williams synthesis of (±)-**2**. Correspondingly, this synthetic sequence represents a formal 10 step (7 step by the longest linear sequence) synthesis of (±)-malbrancheamide B, an improvement over the previous syntheses of (±)-**2** or *ent*-(−)-(**2**).

The racemic synthetic route served to validate our chemistry and helped us to determine optimal conditions for the domino reaction sequence. Our attention was then focused on the analogous asymmetric route using the chiral nonracemic DKP **19** (Scheme 3). This necessary starting material was prepared in four steps from commercially available L-serine methyl ester.[15] The domino reaction sequence with DKP **19** and indole carboxaldehyde **13** proceeded in analogous fashion to deliver the diastereomeric cycloadducts **20a** and **20b** in a 1:2 ratio and 85% combined yield. This result demonstrates that the aminal stereocenter effectively controls the azadiene diastereofacial selectivity during cycloaddition; however, the aminal imparts no noticeable effect on the alkene face selection, as evident by the similar (1:2.3) ratio of C12a diastereomeric products that we observed in the racemic route. Additionally, this ratio is in agreement with numerous cases by Williams and co-workers.

The diastereomeric mixture of cycloadducts **20a** and **20b** could not be effectively separated by chromatography on silica

Scheme 3. Diastereoselective Domino Reaction Sequence Featuring the IMDA



gel. As a result, the mixture was subjected to acidic hydrolysis with an equimolar amount of TsOH·H_2O in CH_2Cl_2 at 0 °C, followed by basification and conversion to the diketopiperazine. Under these conditions, which carefully control the stoichiometry, the BOM indole protecting group could be preserved.[27] Although the lactam diastereomers could be easily separated at this point by chromatography, we found that the major isomer **21b** was less soluble than the corresponding C12a diastereomer, and **21b** could be more easily obtained by selective precipitation from the mixture (60% yield).

With the desired DKP cycloadduct **21b** in hand, four tasks remained to complete the synthesis of **2**: (1) selective reduction of the diketopiperazine to reveal the monoketopiperazine function found in the malbrancheamides, (2) excision of the phenyl aminal auxiliary, (3) extension of C1 (malbrancheamide numbering) by two carbons and cyclization to form the pyrrolidine ring, and (4) removal of BOM indole protection.

In light of these synthetic objectives, selective reduction of the tertiary amide in **21b** with Dibal-H[28] delivered the desired

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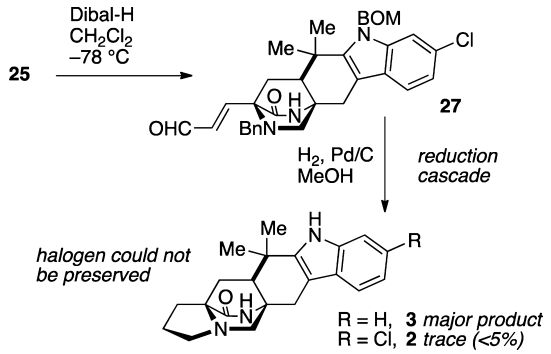
monoketopiperazine and decomposed the aminal auxiliary to reveal the corresponding benzyl amine and C1-alcohol. Oxidation (SO_3·pyr, DMSO, Hünig's base) of the C1-alcohol to the corresponding aldehyde preceded Horner–Wadsworth–Emmons olefination under the soft enolization conditions developed by Masamune and Roush,[29] which delivered the requisite chain extension product. Using either phosphonoamide **23**[30] or phosphonoacetate **24**, products **25** and **26** could be prepared.[31]

The Weinreb amide in **25** was reduced to the α,β-unsaturated aldehyde **27** in preparation for a reduction cascade that we anticipated would reduce the alkene as well as remove both the amine (Bn) and indole (BOM) nitrogen protection (Scheme 4).

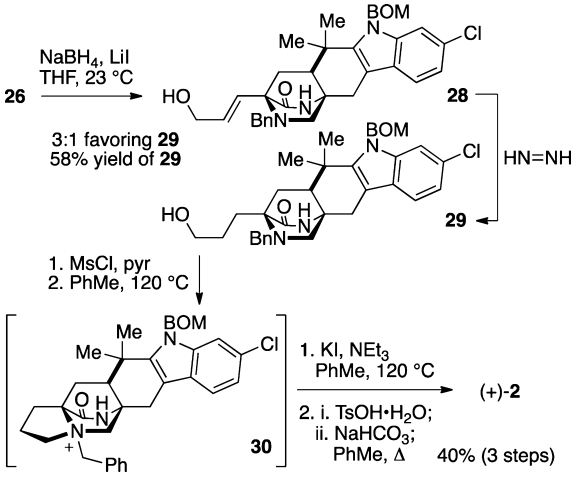
Scheme 4. Catalytic Hydrogenation to the Malbrancheamide Core



The resulting intermediate amino aldehyde would then be poised to undergo cyclization and reductive amination, effecting the final annulation to the pyrrolidine ring and delivering the natural product. In the event, the reduction cascade was capable of forming the pyrrolidine ring and removing the indole protection; however, the C6-indole chlorination proved delicate and could not be preserved under these reaction conditions. Modulation of reaction conditions was met with no success, and premalbrancheamide **3** was consistently observed as the major product.[32] When the duration of reaction was shortened to as little as 5 min, the observed reduction products appeared to lack chlorination as determined by mass spectrometry. In order to circumvent over-reduction and loss of the indole halogen, we turned our attention to an alternative endgame reduction strategy that avoided catalytic hydrogenation.

Toward this end, the α,β-unsaturated ester **26** was prepared in analogous fashion by HWE olefination. We envisioned that 1,4-hydride reduction of **26** followed by iterative 1,2-addition of hydride to the ester moiety would deliver saturated alcohol **29**, an intermediate that we anticipated could be converted to **2** without the use of catalytic hydrogenation (Scheme 5). Sodium borohydride proved competent for this reduction; however, the formation of allylic alcohol **28** was the dominant product (2:1 ratio) under the initial conditions explored (EtOH, THF, 0 → 50 °C). Although formation of **28** could not be entirely avoided, inclusion of LiI as an additive and performing the reaction without protic solvents reversed the dominant product and led to a 3:1 ratio favoring **29**. Following removal of **28** by chromatography, this reaction provided the desired saturated material in 58% isolated yield.[33] Additional quantities of **29** could be prepared from allylic alcohol **28** by reduction with diimide (generated from thermal decomposition of toluenesulfonyl hydrazide in EtOH).[34]

Scheme 5. Completion of the Synthesis of (+)-2



In order to advance toward the target molecule and append the final pyrrolidine ring, the primary alcohol function in **29** was activated as the derived mesylate. This mesylate proved stable at ambient temperatures and was not readily displaced by the nonbonding electrons on the pendant benzyl amine. Heating in toluene (120 °C, sealed tube) achieved the desired intramolecular *N*-alkylation and led to precipitation of quaternary salt **30** from the reaction medium.[35] Addition of KI and NEt_3 to the reaction mixture followed by additional heating led to efficient dealkylation of the benzyl function from the quaternized amine and delivered the malbrancheamide ring system.[36] Using the mild acidic hydrolysis conditions previously described, the N-BOM protection was removed to reveal (+)-**2** in 40% yield from **29** over the three steps. Synthetic (+)-**2** had an identical HPLC retention time as well as matching spectroscopic properties (UV, ^1H and ^{13}C NMR) to an authentic sample of the natural product.

In conclusion, a convergent asymmetric synthesis of (+)-malbrancheamide B was completed in 13 steps as determined by the longest linear route.[37] Additionally, a formal 7 step (LLR) synthesis of (±)-**2** was described. Both racemic and asymmetric synthetic routes feature a domino reaction sequence comprised of an aldol condensation, alkene isomerization and IMDA cycloaddition. This domino reaction sequence and the subsequent chemistry in this manuscript establishes an efficient asymmetric route to [2.2.2]-diazabicyclic prenylated indole alkaloids.

■ EXPERIMENTAL SECTION

Experimental conditions and spectral data were published previously for compounds **13**, **19**, and **20a,b**.[15]

(*S*)-1-Methoxy-6,7,8,8a-tetrahydropyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (14). To a suspension of L-proline methyl ester·HCl (8.04 g, 43 mmol) in CH_2Cl_2 (86.0 mL) at 0 °C was added NEt_3 (12.0 mL, 86 mmol), followed by chloroacetyl chloride (1.1 equiv, 3.72 g, 47 mmol) dropwise via syringe. The reaction mixture was allowed to warm to rt with stirring. After 16 h, the mixture was diluted with sat. aqueous $NaHCO_3$, and the organic layer was removed. The aqueous portion was extracted with CH_2Cl_2 (25 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to afford *N*-chloroacetyl-L-proline methyl ester as a brown oil (7.85 g, 38 mmol). A portion of the resulting oil (5.25 g, 26 mmol) was dissolved in butanone (51 mL) at rt, and NaN_3 (3.67 g, 51 mmol) was added in one portion. The reaction vessel was fitted with a reflux condenser, and the heterogeneous mixture was heated at 80 °C for 20 h. The resulting mixture was filtered and concentrated in vacuo to afford *N*-azidoacetyl-L-proline methyl ester as a red oil (5.37 g, 25 mmol). A

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portion of the oil (1.97 g, 9 mmol) was dissolved in anhydrous PhMe (38 mL), and PPh_3 (2.55 g, 10 mmol) was added in one portion. After gas evolution steadied, the reaction mixture was heated at 90 °C for 20 h. The reaction mixture was concentrated in vacuo and triturated with a 1:1 mixture of Et_2O/hexanes in order to remove the desired DKP from the bulk of phosphine oxide byproduct. The trituration solution was concentrated, and the resulting residue was purified by flash column chromatography on silica gel (elution: 1% MeOH to 10% MeOH in 1:1 EtOAc/PhMe + 1% NEt_3). The resulting diketopiperazine lactim ether product (1.43 g, 8 mmol, 80% yield, 3 steps) was obtained as a light yellow oil: TLC (60% EtOAc in hexane), R_f 0.20 (CAM); $[\alpha]_D^{25}$ = +102 (*c* 2.07, CH_2Cl_2); IR (film) 2951, 2984, 2889, 2360, 2107, 1685, 1457, 1322, 1263, 1022, 751, 673, 625, 573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.21 (dd, *J* = 9.5 Hz, 1.6 Hz, 1H), 4.11 (d, *J* = 4.9 Hz, 1H) 4.03 (m, 1H), 3.68 (s, 3H), 3.65 (m, 1H) 3.47 (m, 1H), 2.25 (m, 1H), 2.03 (m, 1H), 1.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 161.8, 56.5, 53.3, 52.3, 44.2, 29.3, 22.2; Exact mass calcd for $C_8H_{12}N_2O_2$[M + Na^+], 191.0791, found 191.0790. Spectral data for chloroacyl and azidoacyl proline intermediate products are in agreement with published data.[38]

Cycloadducts 17a, 17b, 17c. To diketopiperazine **14** (18 mg, 0.11 mmol) in MeOH (0.1 mL, degassed with nitrogen) at rt in a sealed tube was added **13** (20 mg, 0.05 mmol) and a freshly prepared solution of NaOMe in MeOH (5 equiv, 0.3 mL, 5.0 M). The reaction vessel was heated to 90 °C (bath temperature) for 68 h. After cooling to rt, the reaction mixture was diluted with sat. aqueous NH_4Cl (1 mL) and extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to give a 1.7:1.0:2.9 mixture of cycloadducts **17a**, **17b**, and **17c** as determined by ^1H NMR on the unpurified mixture of products. The residue was purified by flash chromatography on silica gel (elution: 0–5% MeOH in $CHCl_3$) to afford products **17a** (8.0 mg, 29% yield), **17b** (6.0 mg, 22% yield), and **17c** (13.0 mg, 48% yield).

17a: (light yellow oil) TLC (5% MeOH in $CHCl_3$), R_f 0.55 (CAM); IR (film) 1685, 1633, 1476, 1419, 1354, 1324, 1260, 1205, 1179, 1092, 1077, 1055, 1001, 920, 886, 838, 799, 740, 702 cm^{-1}; ^1H NMR (400 MHz, CDCl3) 7.50 (d, *J* = 8.2 Hz, 1H), 7.38–7.30 (m, 5H), 7.19 (s, 1H), 7.10 (dd, *J* = 8.2, 1.6 Hz, 1H), 5.59 (d, *J* = 11.3 Hz, 1H), 5.53 (d, *J* = 11.3 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 3.91 (d, *J* = 17.6 Hz, 1H), 3.71 (s, 3H), 3.54–3.43 (m, 2H), 3.28 (d, *J* = 17.2 Hz, 1H), 2.71–2.64 (m, 1H), 2.41 (dd, *J* = 9.6, 4.1 Hz, 1H), 2.09–1.84 (m, 5H), 1.39 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 170.9, 141.3, 139.3, 137.3, 128.8, 128.2, 128.1, 126.4, 120.6, 120.0, 109.5, 109.4, 73.3, 70.0, 66.8, 64.4, 54.6, 47.6, 43.8, 36.9, 34.5, 29.3, 27.9, 26.4, 24.9, 24.1; Exact mass calcd for $C_{30}H_{32}ClN_3O_3Na$ [M + $Na]^+$, 540.2024, found 540.2017.

17b: (light yellow oil) TLC (5% MeOH in $CHCl_3$), R_f 0.52 (CAM); IR (film) 1678, 1638, 1475, 1419, 1356, 1310, 1265, 1200, 1060, 882, 800, 736, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.46 (d, *J* = 8.2 Hz, 1H), 7.39–7.30 (m, 5H), 7.18 (d, *J* = 1.6 Hz, 1H), 7.09 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.55 (d, *J* = 5.1 Hz, 2H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 3.99 (d, *J* = 16.4 Hz, 1H), 3.80 (s, 3H), 3.51–3.33 (m, 2H), 3.08 (d, *J* = 16.4 Hz, 1H), 2.68–2.66 (m, 1H), 2.34 (dd, *J* = 10.4, 5.1 Hz, 1H), 2.04–1.92 (m, 4H), 1.83 (dd, *J* = 12.9, 5.1 Hz, 1H), 1.42 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 171.3, 140.7, 139.1, 137.1, 128.5, 128.0, 127.9, 125.7, 120.4, 119.6, 109.9, 109.2, 73.1, 69.7, 65.5, 64.3, 54.5, 54.5, 48.8, 43.4, 36.7, 32.8, 29.3, 27.8, 24.8, 21.4; Exact mass calcd for $C_{30}H_{32}ClN_3O_3Na$ [M + $Na]^+$, 540.2024, found 540.2017.

17c: (colorless solid) mp 224.2–225.6 °C; TLC (5% MeOH in $CHCl_3$), R_f 0.50 (CAM); IR (KBr pellet) 3199, 1691, 1475, 1455, 1199, 1098, 1058, 883, 811, 733, 697 cm^{-1}; ^1H NMR (400 MHz, DMSO) 8.76 (s, 1H), 7.57 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.37–7.28 (m, 5H), 7.10 (dd, J = 8.6, 2.0 Hz, 1H), 5.69 (d, J = 10.9 Hz, 1H), 5.64 (d, J = 10.9 Hz, 1H), 4.59 (s, 2H), 3.44 (d, J = 15.6 Hz, 1H), 3.35 (s, 1H), 3.33–3.23 (m, 1H), 2.72 (d, J = 16.0 Hz, 1H), 2.55–2.50 (m, 2H), 2.12–1.81 (m, 5H), 1.36 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 173.0, 168.2, 141.5, 138.6, 137.5, 128.3, 127.7, 127.7, 126.8, 125.0, 120.0, 119.1, 109.8, 107.2, 73.1, 69.0, 66.1, 58.9, 50.2, 43.6, 35.8, 30.5, 28.6, 27.1, 24.0, 23.6, 20.3; Exact mass calcd for $C_{29}H_{30}ClN_3O_3Na$ [M + $Na]^+$, 526.1868, found 526.1862

Oxomalbrancheamide B (18). To a solution of compound **17b** (6 mg, 0.012 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added TsOH·H_2O (6 mg, 0.029 mmol). The solution was allowed to warm to room temperature with stirring, and an additional portion of TsOH·H_2O (6 mg, 0.029 mmol) was added after 2 h. After a total of 4 h, sat. aqueous $NaHCO_3$ (2 mL) was added. The aqueous layer was separated and extracted with EtOAc (4 × 10 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The unpurified residue (4 mg) was dissolved in toluene (1 mL) and heated to 125 °C in a sealed tube with stirring. After 22 h, heat was removed, and the solution was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (elution: 5% MeOH in $CHCl_3$) to afford product **18** (3.0 mg, 61% yield). **18** was also prepared from **17c** as follows: to a solution of compound **17c** (11 mg, 0.021 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added TsOH·H_2O (10 mg, 0.053 mmol). The solution was allowed to warm to room temperature with stirring, and an additional portion of TsOH·H_2O (10 mg, 0.053 mmol) was added after 2 h. After a total of 4 h, sat. aqueous $NaHCO_3$ (2 mL) was added. The aqueous layer was separated and extracted with EtOAc (4 × 10 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The unpurified residue (12.4 mg) was dissolved in toluene (1 mL) and heated to 125 °C in a sealed tube with stirring. After 17 h, heat was removed, and the solution was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (elution: 5% MeOH in $CHCl_3$) to afford product **18** (7.0 mg, 87% yield). Spectral data were in agreement with published data.[21a]

Diketopiperazine 21b. To a solution of compounds **20a** and **20b**[15] (200 mg, 0.34 mmol) in CH_2Cl_2 (33.5 mL) was added TsOH·H_2O (70 mg, 0.37 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, and then sat. aqueous $NaHCO_3$ (2 mL) was added. The aqueous layer was separated and extracted with EtOAc (4 × 10 mL). The unpurified product was a 1:2 ratio of diastereomers as judged by ^1H NMR. The unpurified residue (223.7 mg) was dissolved in toluene (30 mL) and heated to 110 °C. After 19 h, heat was removed, and the solution was concentrated in vacuo. The residue was purified by recrystallization from 25% EtOAc in hexane to afford product **21b** (127 mg, 65% yield) as a colorless amorphous solid: TLC (40% EtOAc in hexane) R_f 0.20 (CAM); $[\alpha]_D^{25}$ = −2.7 (*c* 0.48, MeOH); IR (KBr pellet) 1721, 1690, 1495, 1474, 1453, 1406, 1370, 1311, 1241, 1204, 1109, 1071, 929, 914, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38–7.31 (m, 11H), 7.18 (d, *J* = 1.6 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.42 (s, 1H), 6.22 (s, 1H), 5.55 (d, *J* = 10.9 Hz, 1H), 5.52 (d, *J* = 11.3 Hz, 1H), 4.77 (d, *J* = 9.4 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.14 (d, *J* = 9.8 Hz, 1H), 3.78 (d, *J* = 15.6 Hz, 1H), 2.68 (t, *J* = 7.4 Hz, 1H), 2.66 (d, *J* = 15.6 Hz, 1H), 2.34 (m, *J* = 7.8 Hz, 2H), 1.49 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 166.1, 140.5, 139.1, 136.3, 129.4, 128.6, 128.6, 128.2, 127.9, 126.5, 125.0, 120.8, 119.2, 109.6, 107.2, 89.3, 73.0, 70.0, 68.4, 65.1, 60.8, 50.6, 36.4, 29.9, 27.8, 25.0, 21.0; Exact mass calcd for $C_{34}H_{32}ClN_3O_4Na$ [M + $Na]^+$, 604.1973, found 604.1967.

Aldehyde 22. To a solution of compound **21b** (63 mg, 0.11 mmol) in toluene (1 mL) at 0 °C was added dibal-H (2.10 mL, 1.0 M solution in toluene). The reaction was stirred for 0.5 h at 0 °C, and then EtOAc (2 mL), potassium sodium tartrate tetrahydrate (100 mg), and water (2 mL) were successively added. The biphasic mixture was stirred rapidly for 1 h, and the organic layer was removed. The aqueous layer was extracted with additional EtOAc (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The unpurified product was a single diastereomer as judged by ^1H NMR. The residue was purified by flash chromatography on silica gel (elution: 45–65% EtOAc in hexane) to afford the derived intermediate aminoalcohol (not shown) (49 mg, 80% yield) as a yellow oil. Spectral data were in agreement with published data.[15] A portion of this aminoalcohol material (43 mg, 0.08 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added DMSO (55 μL) and iPr$_2$NEt (100 μL, 0.57 mmol). To this solution was added SO_3·pyridine (0.5 M, 450 μL). The solution was stirred for 30 min at 0 °C and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel

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(elution: 35−100% EtOAc in hexane) to afford product **22** (39 mg, 92% yield) as a yellow oil: TLC (50% EtOAc in hexane) R_f 0.25 (CAM); $[\alpha]_D^{25}$ = +20.9 (*c* 1.0, CH_2Cl_2); IR (film) 1733, 1669, 1475, 1454, 1360, 1318, 1266, 1240, 1202, 1132, 1065, 882, 805, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 10.23 (s, 1H), 7.43−7.18 (m, 11H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.44 (s, 1H), 5.53 (s, 2H), 4.57 (s, 2H), 4.28 (d, *J* = 12.9 Hz, 1H), 3.31 (d, *J* = 12.9 Hz, 1H), 3.23 (d, *J* = 10.9 Hz, 1H), 2.88 (d, *J* = 15.6 Hz, 1H), 2.80 (d, *J* = 15.2 Hz, 1H), 2.29−2.01 (m, 4H), 1.54 (s, 3H), 1.45 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 171.7, 141.2, 138.8, 137.7, 136.7, 128.6, 128.4, 128.4, 128.3 128.2, 127.9, 127.3, 125.0, 120.8, 118.8, 109.7, 106.6, 77.2, 73.0, 70.1, 66.5, 59.4, 59.2, 55.1, 47.3, 35.2, 30.1, 29.5, 28.8, 22.5; Exact mass calcd for $C_{34}H_{34}ClN_3O_3Na$ $[M + Na]^+$, 590.2181, found 590.2184.

Weinreb Amide 25. To a solution of compound **22** (39 mg, 0.069 mmol) in acetonitrile (3.8 mL) was added phosphonamide **23** (34 mg, 0.14 mmol), LiCl (23 mg, 0.54 mmol), and DBU (0.026 mL, 0.17 mmol). The solution was stirred at rt for 1 h, and then H_2O (2 mL) was added. The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (elution: 60−80% EtOAc in hexane) to afford product **25** (27 mg, 60% yield) as a yellow oil: TLC (60% EtOAc in hexane) R_f 0.20 (CAM); $[\alpha]_D^{25}$ = +8.9 (*c* = 0.09, CH_2Cl_2); IR (film) 1682, 1629, 1472, 1455, 1418, 1374, 1313, 1241, 1204, 1131, 1061, 999, 882, 800, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.52−7.13 (m, 14H), 7.05 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.33 (s, 1H), 5.55 (s, 2H), 4.57 (d, *J* = 0.8 Hz, 2H), 4.28 (d, *J* = 13.7 Hz, 1H), 3.68 (s, 3H), 3.27 (s, 3H), 3.27 (d, *J* = 10.9 Hz, 1H), 3.13 (d, *J* = 13.3 Hz, 1H), 2.83 (q, *J* = 15.2 Hz, 2H), 2.30−2.25 (m, 2H), 2.10−2.04 (m, 2H), 1.58 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 143.2, 141.5, 138.9, 138.5, 136.8, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.0, 125.1, 122.0, 120.8, 118.7, 109.8, 106.8, 73.1, 70.2, 62.0, 61.9, 60.1, 59.3, 54.9, 47.8, 35.1, 35.0, 30.3, 30.2, 22.5; Exact mass calcd for $C_{38}H_{41}ClN_4O_4Na$ $[M + Na]^+$, 675.2709, found 675.2702.

Methyl Ester 26. To a solution of compound **22** (110 mg, 0.19 mmol) in acetonitrile (10 mL) was added trimethyl phosphonoacetate **24** (0.065 mL, 0.40 mmol), LiCl (67 mg, 1.60 mmol), and DBU (0.075 mL, 0.50 mmol). The solution was stirred at rt for 1 h, and then H_2O (2 mL) was added. The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give a 3:1 mixture of *E* and *Z* isomers of **26** as shown by ^1H NMR. The residue was purified by flash chromatography on silica gel (elution: 40−100% EtOAc in hexane) to afford product **26** (110 mg, 91% yield) as a yellow oil: TLC (40% EtOAc in hexane) R_f 0.40 (CAM); $[\alpha]_D^{25}$ = +7.9 (*c* 2.4, CH_2Cl_2); IR (film) 1724, 1685, 1608, 1562, 1495, 1475, 1454, 1359, 1308, 1241, 1202, 1174, 1131, 1062, 882, 803, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.51 (d, *J* = 16.4 Hz, 1H), 7.38−7.18 (m, 12H), 7.05 (d, *J* = 8.2, 1H), 6.63 (d, *J* = 16.4 Hz, 1H), 5.55 (s, 2H), 4.60−4.54 (m, 2H), 4.25 (d, *J* = 12.9 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 1H), 3.26 (d, *J* = 10.9 Hz, 1H), 3.13 (d, *J* = 13.3 Hz, 1H), 2.89−2.81 (m, 2H), 2.25−2.05 (m, 4H), 1.58 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 166.8, 145.2, 141.3, 138.8, 138.3, 136.8, 128.6, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.1, 125.0, 124.1, 120.8, 120.7, 118.8, 109.7, 106.8, 77.2, 73.0, 70.1, 61.6, 59.8, 59.3, 54.9, 51.7, 47.8, 35.1, 34.6, 30.3, 30.0, 24.3, 22.4; Exact mass calcd for $C_{37}H_{38}ClN_3O_4Na$ $[M + Na]^+$, 646.2443, found 646.2436.

Premalbrancheamide (3). To a solution of compound **25** (26 mg, 0.39 mmol) in PhMe (1 mL) at −78 °C was added a solution of dibal-H (1.0 M in PhMe, 0.20 mL). The solution was stirred for 1 h, and then MeOH (1 mL), HCl (1 mL), EtOAc (1 mL), and potassium sodium tartrate·$4H_2O$ (50 mg) was added. After an additional 1 h of stirring, the aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was quickly purified by flash chromatography on silica gel (elution: 40−100% EtOAc in hexanes) to afford product **27** (15.5 mg, 67% yield) as a light yellow oil. Aldehyde **27** was unstable and prone to decomposition; accordingly, the product was used immediately in the following reduction sequence. To a solution of compound **27** (7.0 mg, 0.015 mmol) in MeOH (1.0 mL) was added Pd/C (17 mg) at rt. The solution was sparged with H_2. After 5 min, the H_2 was stopped and Ar was bubbled through the solution. The suspension was filtered through Celite and concentrated in vacuo to afford a mixture containing predominantly product **3** (4.0 mg, 65% yield): TLC (80% EtOAc in hexane) R_f 0.25 (CAM). Spectral data for **3** were in agreement with published data.[18,23]

Saturated Alcohol 29. To a solution of compound **26** (36 mg, 0.059 mmol) in THF (1.0 mL) at 0 °C was added $NaBH_4$ (24 mg, 0.64 mmol) and LiI (76 mg, 0.57 mmol). The solution was warmed to rt, and additional $NaBH_4$ and LiI (10 equivalents each) were added in three portions after successive 12 h increments. After 48 h, sat. aqueous NH_4Cl (1 mL) was added. The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give a 1:3 mixture of alcohols **28** and **29** as shown by ^1H NMR. The residue was purified by flash chromatography on silica gel (elution: 50−100% EtOAc in hexanes) to afford product **29** (20. mg, 58% yield) as a white solid: mp 92.7−94.2 °C; TLC (60% EtOAc in hexane), R_f 0.15 (CAM); $[\alpha]_D^{25}$ = +1.4 (*c* 0.85, CH_2Cl_2); IR (film) 1740, 1672, 1473, 1453, 1359, 1318, 1240, 1205, 1059, 882, 802, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.40−7.13 (m, 12H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.56 (s, 1H), 5.54 (s, 2H), 4.56 (s, 2H), 4.27 (d, *J* = 12.9 Hz, 1H), 3.78−3.72 (m, 2H), 3.11 (d, *J* = 10.9 Hz, 1H), 3.06 (d, *J* = 12.5 Hz, 1H), 2.81 (d, *J* = 15.6, 1H), 2.76 (d, *J* = 15.2, 1H), 2.48 (s, 1H), 2.27 (dd, J_1 = 13.3, J_2 = 4.3 Hz, 1H), 2.20 (d, *J* = 11.3 Hz, 1H), 2.07−1.98 (m, 2H), 1.93 (d, *J* = 11.7, 2H), 1.88−1.83 (m, 2H), 1.52 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 141.6, 138.8, 138.5, 136.8, 128.6, 128.4, 128.3, 128.2, 127.9, 127.0, 125.1, 120.8, 118.7, 109.7, 106.8, 77.2, 73.1, 70.1, 62.7, 60.2, 59.6, 57.3, 54.5, 47.3, 35.1, 30.4, 30.2, 30.1, 26.9, 26.4, 22.3; Exact mass calcd for $C_{36}H_{40}ClN_3O_3Na$ $[M + Na]^+$, 620.2650, found 620.2643. Alcohol **29** can also be prepared from **28** as follows. To a solution of compound **28** (6.0 mg, 0.0092 mmol) in EtOH (0.4 mL) at rt was added 4-methylbenzene sulfonhydrazide (2 mg, 0.010 mmol) and NaOAc (1 mg, 0.010 mmol). The solution was heated to reflux, and additional portions (0.010 mmol) of sulfonhydrazide and NaOAc were added after 2 h. After 6.5 h at reflux, heat was removed, and the solution was concentrated in vacuo. Sat. aqueous Na_2CO_3 (2 mL) and EtOAc (2 mL) were added to the residue, and the aqueous layer was separated and extracted with additional EtOAc (3 × 5 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography according to the above procedure to afford **29** (3.3 mg, 60% yield) as a white solid.

Malbrancheamide B (2). To a solution of compound **29** (24 mg, 0.040 mmol) in CH_2Cl_2 (0.4 mL) at 0 °C was added pyridine (6.3 μL, 0.079 mmol) and MsCl (3.4 μL, 0.043 mmol). The solution was allowed to warm to rt with stirring, and additional portions of MsCl (3.4 μL, 0.043 mmol) were added every 3 h. After a total of 12 h, sat. aq. $NaHCO_3$ (2 mL) was added. The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue (22 mg) was dissolved in toluene (2 mL) and heated to 125 °C in a sealed tube with stirring. After 10 h, heat was removed, and the solution was concentrated in vacuo. To a solution of the unpurified residue (18 mg) in toluene (1.5 mL) was added KI (6.0 mg, 0.035 mmol) and NEt_3 (0.15 mL) in a sealed tube. The solution was heated to 125 °C and stirred for 20 h. After 20 h, heat was removed, and the solution was concentrated in vacuo. To a solution of the unpurified residue (13 mg) in CH_2Cl_2 (2.6 mL) was added TsOH·H_2O (15.8 mg, 0.083 mmol) at 0 °C. The solution was allowed to warm to rt with stirring, and an additional portion of TsOH·H_2O (14 mg, 0.072 mmol) was added after 2 h. After a total of 4 h, $NaHCO_3$ (2 mL) was added. The aqueous layer was separated and extracted with EtOAc (4 × 10 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The product was purified by flash chromatography on silica gel (elution: 0−10% MeOH in $CHCl_3$) to afford product **2** (6.0 mg, 40% yield) as an amorphous colorless solid: TLC (5% MeOH in $CHCl_3$), R_f 0.50 (CAM); $[\alpha]_D^{25}$ = +25 (*c* 0.4, MeOH), Lit.[16] $[\alpha]_D$ = +50 (*c* 1, MeOH), Lit.[22] (−)-**2**, $[\alpha]_D$ = −36 (*c* 0.81, MeOH), Lit.[17] $[\alpha]_D$ = +28 (*c* 0.5, MeOH); HPLC trace and UV signature identical for both synthetic and an authentic natural sample of

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2; Mobile phase, gradient mixture of H_2O + 0.1% TFA/MeCN, 1.0 mL/min; 0−10 min 20% MeCN, 10.01−20 min 20−50% MeCN); Phenomenex C18 Luna (250 mm × 4.6 mm × 5 μm), retention time 15.17 min; UV λ 230, 283 nm; IR (film) 1653, 1465, 1361, 1319, 1291, 1253, 1227, 1198, 1131, 1099, 1059, 1024, 904, 797 cm^{-1}; Exact mass calcd for $C_{21}H_{24}ClN_3O$ $[M + H]^+$, 370.1681, found 370.1677. ^1H and ^{13}C NMR spectral data for synthetic material both match the data for the authentic sample and are in agreement with published data.[21,22,16b]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectroscopic data and experimental details for the preparation of all new compounds as well as ^1H NMR and ^{13}C NMR spectra. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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