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Transformations of the 2,7-*Seco Aspidosperma* Alkaloid Leuconolam, Structure Revision of *epi*-Leuconolam, and Partial Syntheses of Leuconoxine and Leuconodines A and F

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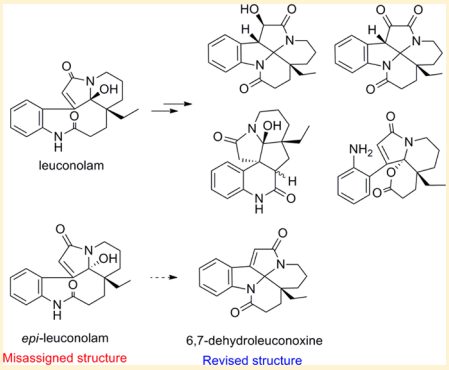
Supporting Information

ABSTRACT: Several transformations of the *seco Aspidosperma* alkaloid leuconolam were carried out. The based-induced reaction resulted in cyclization to yield two epimers, the major product corresponding to the optical antipode of a (+)-meloscine derivative. The structures and relative configuration of the products were confirmed by X-ray diffraction analysis. Reaction of leuconolam and *epi*-leuconolam with various acids, molecular bromine, and hydrogen gave results that indicated that the structure of the alkaloid, previously assigned as *epi*-leuconolam, was incorrect. This was confirmed by an X-ray diffraction analysis, which revealed that *epi*-leuconolam is in fact 6,7-dehydroleuconoxine. Short partial syntheses of the diazaspiro indole alkaloid leuconoxine and the new leuconoxine-type alkaloids leuconodines A and F were carried out.



The 2,7-*seco Aspidosperma* alkaloid leuconolam (**1**) and its C-21 epimer, *epi*-leuconolam (**2**), which are related to the known rhazinilam,[1] were first isolated from the bark extract of *Leuconotis griffithii*.[2] Subsequently, the related diazaspiro pentacyclic alkaloid leuconoxine (**3**) was reported from the Indonesian *L. eugenefolia*,[3] and other rhazinilam/leuconolam alkaloids were also found to occur in other genera of the *Apocynaceae* such as *Kopsia*.[4] These alkaloids include rhazinal,[5] rhazinicine,[6] and arboloscine.[7] Another alkaloid with a new tetracyclic skeleton incorporating a tetrahydro-2*H*-azepine moiety was mersicarpine (**4**), which was isolated from *Kopsia*[8] and *Leuconotis*.[9] A speculative biosynthetic pathway has been suggested from a leuconolam precursor,[8] and several total syntheses of this alkaloid have also been reported.[10] In addition, a number of new rhazinilam, leuconolam, and leuconoxine alkaloids (leuconodines A–E) have been reported from *Leuconotis*.[9] Since leuconolam (**1**) was available from our ongoing work on *Kopsia* and *Leuconotis* alkaloids,[8,9] it offered the opportunity to explore the chemistry of this unusual indole compound, characterized by a 2,7-*seco Aspidosperma* carbon skeleton.

It was reported that the reaction of leuconolam (**1**) with KOH in EtOH/MeOH gave the cyclized product **6** [the enantiomer of a derivative of (+)-meloscine (**5**)][11] as the sole product in high yield.[2c] As no evidence was presented to support the stereochemical assignments, we reinvestigated this transformation. When the reaction was repeated by the use of stronger bases such as NaOMe/MeOH or NaHMDS/THF, the reaction did not proceed and led only to the recovery of starting material. When using the conditions employed in the earlier report (KOH in EtOH/MeOH at rt for 6 h), compounds **6** and **7** were formed in 12% and 3% yields, respectively, and these were also accompanied by unreacted **1** (20%).[12]

The major product **6** was obtained as a colorless oil and subsequently as colorless block crystals (mp 266–268 °C) from CCl_4/MeOH, with $[\alpha]^{25}_D$ = −198 (*c* 0.06, $CHCl_3$). The UV spectrum showed absorption maxima at 210, 253, and 287 nm, indicating the presence of a dihydroquinolone chromophore,[11] while the IR spectrum showed the presence of OH (3226 cm^{-1}) and lactam carbonyl functions (1667 cm^{-1}). The ESIMS of **6** showed an $[M + H]^+$ ion at *m*/*z* 327, and HRESIMS measurements gave the molecular formula as $C_{19}H_{22}N_2O_3$ + H. The ^1H and ^{13}C NMR data of **6** were similar to those reported earlier.[2c] The attachment of C-16 to C-7 was supported by the observed three-bond correlation from H-16 to C-6 in the HMBC spectrum, while the α-orientation of H-16 was assigned from the NOE enhancement between H-6α and H-16. The minor product **7** was obtained as a colorless oil and subsequently as colorless block crystals (mp 250–252 °C) from CH_2Cl_2/hexanes, with $[\alpha]^{25}_D$ = −150 (*c* 0.01, $CHCl_3$). The UV (210, 251, 306 nm) and IR data (3322, 1712, 1667 cm^{-1}) were similar to those of **6**, while the ESIMS showed that **7** was isomeric with **6**. A major difference in the NMR data of **7** compared with those of the major product **6** was the notable absence of an NOE between H-6α and H-16, which suggested the β-orientation of H-16 in **7**. Since suitable crystals of both **6**

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and **7** were obtained, X-ray diffraction analyses were carried out, which confirmed the structures and relative configurations assigned based on the NMR data (Figure 1).

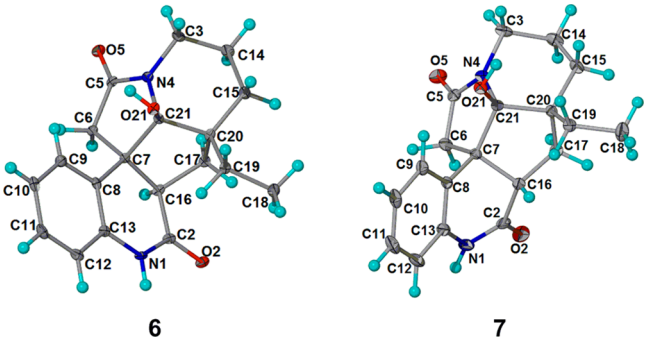


Figure 1. X-ray crystal structures of **6** and **7**.

The formation of **6** and **7** can be rationalized based on an intramolecular Michael addition from the presumably more stable *E*-enolate, which approaches the *si*-face of C-7 to form the major product **6**, while the minor product **7** resulted from attack by the presumably less stable *Z*-enolate to the same *si*-face of C-7 (Scheme 1).

It was initially envisaged that treatment of leuconolam (**1**) with acid should result in a facile transannular closure to give a dehydroleuconoxine derivative, which could serve as a possible starting compound for further elaboration to leuconoxine (**3**) and its recently discovered congeners, leuconodines A–E,[9] or to mersicarpine (**4**).[8,9]

Treatment of leuconolam (**1**) with aqueous HCl (5%, rt, 12 h) did not result in any reaction, leading only to recovery of starting material upon basification (Table 1). When the same reaction was carried out in a two-phase medium in the presence of a phase-transfer catalyst (tetraethylammonium chloride, TEACl), both *epi*-leuconolam (**2**) (47%) and unreacted leuconolam (**1**) (35%) were obtained. Examination of the product mixture revealed the formation of a minor product (compound **A**), with a yield of 1.4%. Repeating the two-phase experiment (5% HCl/CH_2Cl_2, TEACl) with *epi*-leuconolam (**2**) resulted in the isolation of leuconolam (**1**) (15%) and *epi*-leuconolam (**2**) (84%).

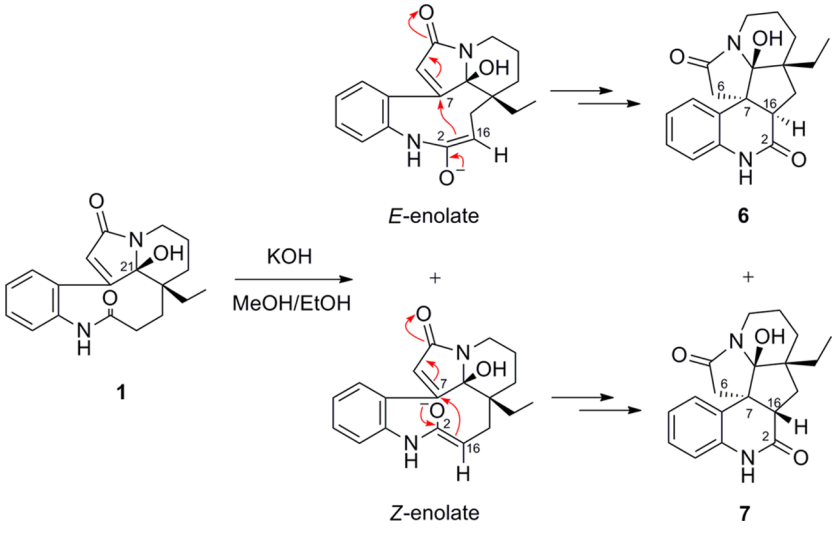
Table 1. Transformations of Leuconolam (1) and its Supposed C-21 Epimer (*epi*-Leuconolam, 2) Under Various Conditions

			products			
entry	starting material	reaction conditions	**1**	**2**	compound **A**	**8**
1	**1**	5% HCl, rt, 8 h	no reaction (recovery of **1** on basification)			
2	**1**	5% HCl/CH_2Cl_2 + TEACl, rt, 14 h[a]	35%	47%	1.4%	
3	**1**	HCl/MeOH, rt, 12 h	4%			63%
4	**1**	CSA/CH_2Cl_2, rt, 14 h[a]	10%	62%	2%	
5	**1**	CSA/CH_2Cl_2, rt, 11 h (4 equiv MeOH added)		19%		54%
6	**1**	CSA/MeOH, rt, 14 h	4%		2%	94%
7	**1**	PTSA/MeOH, rt, 14 h	4%		0.8%	94%
8	**1**	PTSA/CH_2Cl_2, rt, 14 h	3%	5%	42%	
9	**2**	5% HCl/CH_2Cl_2 + TEACl, rt, 12 h[a]	15%	84%		
10	**2**	CSA/CH_2Cl_2, rt, 15 h	no reaction[b]			
11	**2**	PTSA/CH_2Cl_2, rt, 10 h		1%	70%	
12	**8**	PTSA/CH_2Cl_2, rt, 10 h	no reaction[c]			
13	**1**	H_2, Pd/C	no reaction			
14	**2**	H_2, Pd/C	**3** (90%)			
15	**1**	Br_2/$CHCl_3$	**13** (86%)			
16	**2**	Br_2/$CHCl_3$	**13** (96%)			

[a]Prolonged reaction time leads to reduced overall yields. [b]Traces of **1** and compound **A** detected from TLC. [c]Traces of **1** and **2** detected from TLC.

When leuconolam (**1**) was treated with 10-camphorsulfonic acid (CSA) in anhydrous CH_2Cl_2, *epi*-leuconolam (**2**) was

Scheme 1. Formation of 6 and 7



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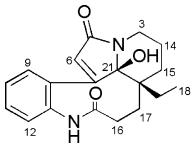
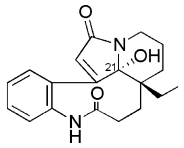
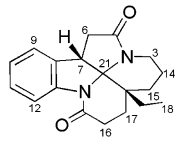
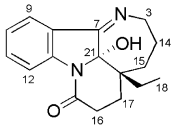
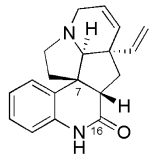

1 leuconolam


2 *epi*-leuconolam


3 leuconoxine


4 mersicarpine


5 (+)-meloscine

obtained in a yield of 62%, accompanied by 2% of the previously noted minor product (compound **A**). Similar treatment of **1** with CSA in anhydrous MeOH resulted in the formation of *O*-methylleuconolam (**8**)[2c] in 94% yield, accompanied by 2% of compound **A**. Treatment of **1** with concentrated HCl (a few drops) in anhydrous MeOH gave only **8** in a reduced yield of 63%. Treatment of **1** with *p*-toluenesulfonic acid (PTSA) in anhydrous MeOH also yielded the *O*-methyl derivative **8** as the major product (94%) with compound **A** detected as the minor product (1%).

When leuconolam (**1**) was treated with PTSA in anhydrous CH_2Cl_2, an inversion in the product distribution was noted, with compound **A** obtained as the major product (42%) and *epi*-leuconolam (**2**) as the minor product (5%). These results are summarized in Table 1.

The results of the transformations of leuconolam (**1**) and *epi*-leuconolam under various conditions as summarized in Table 1 presented some puzzling features. The formation of *epi*-leuconolam (**2**) and leuconolam (**1**) when leuconolam (**1**) or *epi*-leuconolam (**2**) was treated with aqueous acid under two-phase conditions (entries 2 and 9, Table 1) suggested the possibility that the products are derived via reversible formation of the *N*-4−C-21 iminium ion **9**, followed by solvolysis to give a mixture of **2** and **1**, with **2** (*epi*-leuconolam) predominating in both instances. This would appear to suggest that **2** was the thermodynamically more stable product under such conditions. When the acid-induced reaction was carried out in MeOH (entries 3, 6, and 7, Table 1) in the presence of either HCl, CSA, or PTSA, virtually quantitative conversion to *O*-methylleuconolam (**8**, 21β-OMe) was observed, suggesting efficient trapping of the iminium ion from the β-face by MeOH. The exclusive formation of the C-21 β-oriented methyl ether is puzzling, especially since the α-OH epimer (*epi*-leuconolam, **2**) appeared to be the thermodynamically preferred product. Another discrepancy was noted when comparing entries 4 and 10, Table 1. The reaction of leuconolam (**1**) with CSA in CH_2Cl_2 gave *epi*-leuconolam (**2**) as the major product, but when *epi*-leuconolam (**2**) was exposed to the same conditions, no reaction occurred (cf. entries 2 and 9, Table 1).

Other inconsistencies were subsequently noted for the hydrogenation and bromination reactions of leuconolam (**1**) and *epi*-leuconolam (**2**). For instance, while *epi*-leuconolam (**2**) was smoothly hydrogenated, leuconolam (**1**) was, by comparison, unreactive (entries 13 and 14, Table 1), whereas in the case of the bromination reaction, both **1** and **2** reacted to give the same bromine addition product (entries 15 and 16, Table 1). Furthermore debromination (Zn/AcOH) of the dibromide apparently yielded *epi*-leuconolam (**2**). These puzzling and apparently inconsistent results led to a reevaluation of the earlier structure elucidation for leuconolam (**1**) and *epi*-leuconolam (**2**).

epi-Leuconolam was first isolated as a minor alkaloid from *L. griffithii* and *L. eugenefolia*.[2c] It has subsequently been detected as a minor alkaloid in *Kopsia griffithii*.[13] The structure was assigned as the C-21 epimer of leuconolam (i.e., **2**) based on EIMS and NMR data. In the initial report, the EIMS apparently showed an $[M]^+$ ion at m/z 326, which was also the base peak and which analyzed for $C_{19}H_{22}N_2O_3$ by HREIMS, indicating an isomeric relationship with leuconolam (**1**).[2c,14] This was confirmed by a subsequent independent EIMS measurement on a different instrument, which also showed the $[M]^+$ ion as a base peak at m/z 326 and which also analyzed for $C_{19}H_{22}N_2O_3$.[13,15] In both instances, a strong $[M - H_2O]^+$ ion at m/z 308 was also detected. The ^{1}H NMR spectrum showed features that in many ways indicated the isomeric relationship with leuconolam (**1**). A sharp singlet at δ_H 6.02 showed the presence of an isolated olefinic proton corresponding to H-6, while the triplet centered at δ_H 0.76 indicated the presence of an ethyl substituent. A notable difference observed in the ^{1}H NMR spectrum of *epi*-leuconolam (**2**) when compared with that of **1**, however, was the absence of the characteristic indolic *N*H and C-21-OH resonances. The ^{13}C NMR spectrum of *epi*-leuconolam accounted for the 19 carbons and showed a close similarity to the spectrum of leuconolam (**1**) except for small differences in the chemical shifts.[2c]

Since the structure of leuconolam (**1**) rested firmly on an X-ray diffraction analysis, which we have repeated,[16] we reinvestigated the structure assignment of *epi*-leuconolam using a natural sample from our concurrent work in the alkaloid field.[9]

LC-ESIMS analysis of *epi*-leuconolam (**2**) gave an $[M + H]^+$ ion at m/z 309, which indicated a molecular ion (m/z 308) 18 mass units less than that obtained previously by EIMS. HRESIMS gave the formula $C_{19}H_{20}N_2O_2$ + H. Banwell and co-workers have also reported syntheses of rhazinal, rhazinilam, leuconolam (**1**), and *epi*-leuconolam (**2**).[17,18] The latter two compounds were obtained by oxidation of rhazinilam (excess PCC, 18 °C, 4 Å molecular sieves), followed by aqueous workup (EtOAc/MeOH/H_2O) of the reaction mixture.[18] The EIMS of the synthetic *epi*-leuconolam (**2**) showed a base peak at m/z 308, with the m/z 326 ion detected as a weak peak (<1%). In the original report, it was noted that the IR spectrum of *epi*-leuconolam (**2**) showed a strong broad absorption at 3400 cm^{-1} attributed to *N*H and OH.[2c] The IR spectra of *epi*-leuconolam (**2**) and leuconolam (**1**) recorded by us indicated that the IR spectrum of leuconolam (**1**) had a broad absorption at ca. 3260 cm^{-1}, but that *epi*-leuconolam (**2**) did not show any significant absorption in the 3400 cm^{-1} region (the same result was obtained by Banwell and co-workers[18]). In addition, the UV spectra of leuconolam (**1**) (207, 220, 287 nm) and *epi*-leuconolam (**2**) (203, 252, 350 nm) were markedly different, indicating the presence of different chromophores.

The ^{1}H and ^{13}C NMR data of *epi*-leuconolam (**2**) have been reported on a number of occasions and were consistently in agreement with those of the original report.[2c,13,18] We have also carried out additional 2D NMR experiments (COSY, HMQC, HMBC) for *epi*-leuconolam (**2**), which indicated the presence of similar correlations to those in leuconolam (**1**).

In view of the above results, we carried out an X-ray diffraction analysis of the alkaloid that has to date been assigned as *epi*-leuconolam (**2**) (natural sample; suitable crystals were obtained from a CH_2Cl_2/hexanes solution). The X-ray

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diffraction analysis revealed that the alkaloid previously assigned as "*epi*-leuconolam (**2**)" is in fact 6,7-dehydroleuconoxine (**10**) (Figure 2). The molecular ion at *m*/*z* 326 in EIMS

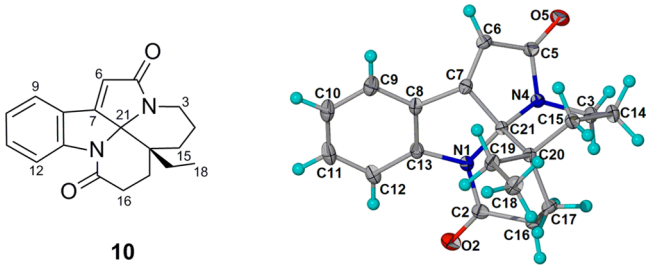
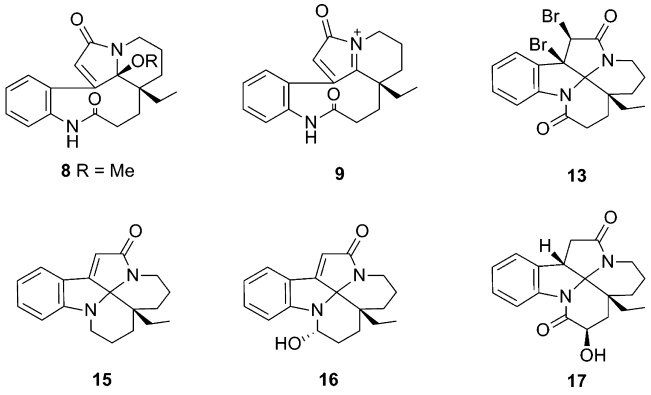


Figure 2. X-ray crystal structure of **10**.

was probably an artifact due to facile cleavage of the initially formed molecular ion followed by facile capture by water present as a contaminant in the sample. The presence of adventitious water probably also accounts for the observation of the broad absorption at 3400 cm^{-1} in the IR spectrum, which was attributed to the presence of *N*H/OH groups, while the revised structure, 6,7-dehydroleuconoxine (**10**), is now compatible with the UV spectrum. The revised structure also accounted for Banwell's transformation of rhazinilam to leuconolam (**1**) and "*epi*-leuconolam" (or 6,7-dehydroleuconoxine (**10**)),[18] since the use of excess PCC followed by the aqueous workup resulted in an acidic medium, which triggered the transannular cyclization of leuconolam (**1**) to 6,7-dehydroleuconoxine (**10**).



With the problem regarding the misassigned structure of "*epi*-leuconolam" resolved, we subsequently focused on the structure of compound **A**, obtained in the acid-induced transformations of leuconolam (**1**).

Compound **A**, eventually assigned structure **11**, was obtained as a yellowish oil and subsequently as yellowish block crystals from CH_2Cl_2/hexanes (mp 179−182 °C) with $[\alpha]^{25}_D$ = +116 (*c* 0.5, $CHCl_3$). The UV spectrum showed absorption maxima at 212, 240, and 340 nm, while the IR spectrum showed the presence of NH_2 (3483 and 3397 cm^{-1}) and carbonyl functions (1743 and 1709 cm^{-1}). The EIMS of compound **A** showed an $[M]^+$ ion at *m*/*z* 326, while HREIMS measurements gave the molecular formula $C_{19}H_{22}N_2O_3$.

The ^{13}C NMR spectrum accounted for all 19 carbon resonances and confirmed the presence two carbonyl functions at δ_C 166.8 (lactam carbonyl) and 170.6 (lactone carbonyl), in addition to a low-field quaternary resonance (δ_C 102.1) due to C-21, which is α to both a nitrogen and an oxygen atom. The ^1H NMR spectrum showed resonances due to four contiguous aromatic hydrogens (δ_H 6.65, 6.66, 6.96, and 7.09) corresponding to an *ortho*-disubstituted aromatic moiety, one olefinic proton (δ_H 6.14), and a broad two-proton singlet due to an amino group, NH_2 (δ_H 3.94, exchangeable with D_2O). The COSY and HMQC data showed the presence of $NCH_2CH_2CH_2$, $C{=}OCH_2CH_2$, and CH_2CH_3 partial structures, as well as an isolated olefinic hydrogen, corresponding to H-6 (Figure 3). Comparison of the NMR data of compound **A**

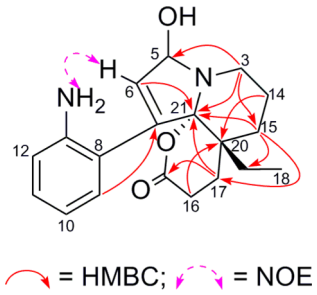


Figure 3. Selected HMBCs and NOE of **11**.

with those of the starting leuconolam (**1**) indicated that the *N*-4−C-5−C-6, *N*-4−C-3−C-14−C-15, and C-16−C-17−C=O partial structures, as well as the C-20 ethyl side chain, have remained intact. The attachment of C-5, C-3, and C-21 to *N*-4 was supported by the observed correlations (HMBC, Figure 3) from H-6 and H-3 to C-21 (low-field quaternary resonance at δ_C 102.1). The observed three-bond correlations from H-15 to C-17, C-19, and C-21 indicated attachment of C-15, C-17, and C-19 to the quaternary C-20, as well as the attachment of C-20 to C-21. The assembly of the molecule is completed by cleavage of the *N*-1 amide function (e.g., in **1**) to a free primary amine and attachment of the carboxylic oxygen to C-21, to reveal the amino lactam-lactone as shown in **11**.

In order to provide proof of the proposed structure, X-ray diffraction analysis was carried out, which confirmed the structure proposed and defined the absolute configuration, as shown in Figure 4. The crystal structure showed that the NH_2

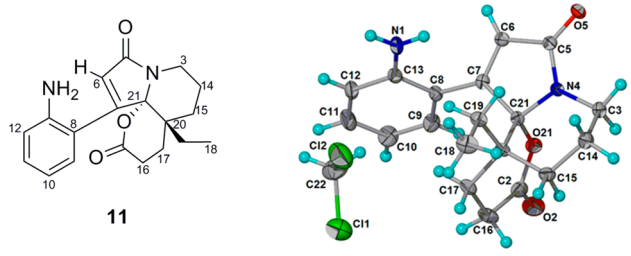


Figure 4. X-ray crystal structure of **11**.

group is oriented away from the lactone moiety and proximate to the olefinic H-6, which was also supported by the observed reciprocal NOEs observed between NH_2 and H-6 (Figure 3).

With the structure of 6,7-dehydroleuconoxine (**10**), previously misassigned as *epi*-leuconolam (**2**), and that of compound **A** (**11**) firmly established, the results of the transformations of leuconolam (**1**) and 6,7-dehydroleuconoxine (**10**) under various conditions become intelligible (Table 2).

The formation of 6,7-dehydroleuconoxine (**10**) with recovered leuconolam (**1**), when leuconolam (**1**) was treated with aqueous acid under two-phase conditions (entry 2, Table 2), presumably derives from reversible formation of the *N*-4−

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Table 2. Transformations of Leuconolam (1) and 6,7-Dehydroleuconoxine (10) Under Various Conditions

entry	starting material	reaction conditions	products			
			1	**10**	**11**	**8**
1	**1**	5% HCl, rt, 8 h	no reaction (recovery of **1** on basification)			
2	**1**	5% HCl/CH_2Cl_2 + TEACl, rt, 14 h[a]	35%	47%	1.5%	
3	**1**	HCl/MeOH, rt, 12 h	4%			63%
4	**1**	CSA/CH_2Cl_2, rt, 14 h[a]	10%	62%	2%	
5	**1**	CSA/CH_2Cl_2, rt, 11 h (4 equiv MeOH added)		19%		54%
6	**1**	CSA/MeOH, rt, 14 h	4%		2%	94%
7	**1**	PTSA/MeOH, rt, 14 h	4%		0.8%	94%
8	**1**	PTSA/CH_2Cl_2, rt, 14 h	3%	5%	42%	
9	**10**	5% HCl/CH_2Cl_2 + TEACl, rt, 12 h[a]	15%	84%		
10	**10**	CSA/CH_2Cl_2, rt, 15 h	no reaction[b]			
11	**10**	PTSA/CH_2Cl_2, rt, 10 h		1%	70%	
12	**8**	PTSA/CH_2Cl_2, rt, 10 h	no reaction[c]			
13	**1**	H_2, Pd/C	no reaction			
14	**10**	H_2, Pd/C	**3** (90%)			
15	**1**	Br_2/$CHCl_3$	**13** (86%)			
16	**10**	Br_2/$CHCl_3$	**13** (96%)			

[a]Prolonged reaction time leads to reduced overall yields. [b]Traces of **1** and compound **A** detected from TLC. [c]Traces of **1** and **9** detected from TLC.

C-21 iminium ion **9**, followed by transannular cyclization to the spirocyclic dehydroleuconoxine (**10**). The reversible nature of this reaction is indicated by the formation of **1** with recovered **10**, when **10** was subjected to the same reaction conditions (entry 9, Table 2). When the acid-induced reaction was carried out in the polar, protic, nucleophilic MeOH (entries 3, 6, and 7, Table 2) in the presence of either HCl, CSA, or PTSA, virtually quantitative conversion to *O*-methylleuconolam (**8**) was observed, suggesting efficient trapping of the iminium ion from the β-face by the larger and more nucleophilic MeOH. With the larger and more nucleophilic MeOH, approach from the less hindered convex β-face is overwhelmingly favored, and the nucleophilic addition step is virtually irreversible; the *O*-methylleuconolam (**8**) once formed was stable under the reaction conditions (**8** did not react when exposed to acid, entry 12, Table 2).

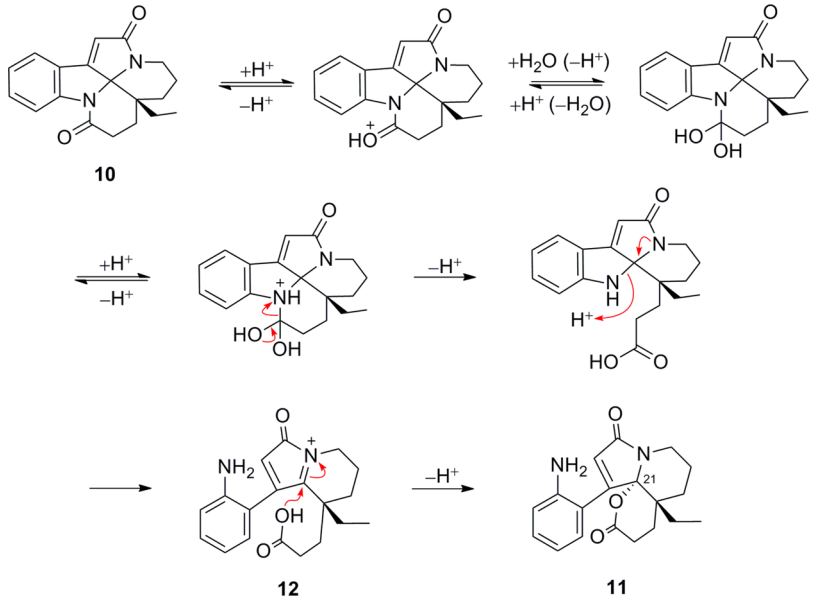
When the reaction was carried out in PTSA/CH_2Cl_2, a change in the product distribution was observed, with the amino lactam-lactone **11** obtained as the major product (42%) and 6,7-dehydroleuconoxine (**10**) as the minor product (5%) (entry 8, Table 2). TLC monitoring of the progress of the reaction showed that the amino lactam-lactone **11** was formed subsequent to the formation of **10**, suggesting that **11** originated from the first-formed **10**. Further confirmation was provided by the observation that treatment of **10** with PTSA/CH_2Cl_2 resulted in the formation of the amino lactam-lactone **11** as the major product in 70% yield (entry 11, Table 2).

A possible pathway for this transformation is shown in Scheme 2, involving acidic hydrolysis of the *N*-1 lactam, followed in succession by fragmentation to the iminium ion **12**, and finally facile intramolecular capture of the iminium ion **12** by the carboxylic acid group, leading eventually to the amino lactam-lactone **11**. The fact that the starting 6,7-dehydroleuconoxine (**10**) is more strained than the product **11** constitutes additional support for the proposed amide hydrolysis under relatively mild conditions.

In view of the facile acid-induced transannular cyclization of leuconolam (**1**) to 6,7-dehydroleuconoxine (**10**), a two-step sequence involving acid-induced cyclization (CSA/CH_2Cl_2) followed by hydrogenation (H_2, Pd/C) yielded leuconoxine (**3**) in ca. 55% overall yield from leuconolam (**1**). This transformation represents a partial synthesis of leuconoxine (**3**) from leuconolam (**1**). Leuconoxine (**3**) was previously obtained by bioconversion of rhazinilam with *Beauveria bassiana* LMA (ATCC 7159), but in low yield (0.6%).[19]

During the course of the present study, an alkaloid corresponding to 6,7-dehydroleuconoxine (**10**) (NMR data identical to "*epi*-leuconolam" or 6,7-dehydroleuconoxine) was reported as a minor alkaloid from the stem-bark extract of

Scheme 2. Possible Pathway for the Formation of 11 from 10



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Melodinus henryi.[20] In view of the above, the possibility that this alkaloid is an artifact due to the action of traces of acid on leuconolam (**1**) cannot be discounted.

Treatment of leuconolam (**1**) with Br_2 in $CHCl_3$ gave the dibromoleuconoxine derivative 6*β*,7*β*-dibromoleuconoxine (**13**) as the sole product in about 90% yield (Table 2).[2c] Monitoring of the progress of the bromination reaction by TLC indicated that two products, in addition to the starting leuconolam (**1**), were detected at an early stage of the reaction. These were 6*β*,7*β*-dibromoleuconoxine (**13**) and 6,7-dehydroleuconoxine (**10**). This observation suggested a two-step sequence involving transannular cyclization to **10**, followed by bromine addition to furnish **13**. This was supported by the observation that treatment of 6,7-dehydroleuconoxine (**10**) with $Br_2/CHCl_3$ proceeded smoothly to yield the same dibromoleuconoxine product **13**. Monitoring of the reaction progress by TLC showed only the presence of 6,7-dehydroleuconoxine (**10**) and the dibromoleuconoxine addition product, **13**. Furthermore, debromination (Zn/AcOH) of the dibromo addition product led smoothly to 6,7-dehydroleuconoxine (**10**).

6*β*,7*β*-Dibromoleuconoxine (**13**) was obtained as a white, amorphous solid, with $[\alpha]^{25}_D$ = −38 (*c* 0.6, $CHCl_3$). The UV spectrum showed absorption maxima at 208, 227, and 292 nm, while the IR spectrum showed the presence of two lactam carbonyls at 1691 and 1709 cm^{-1}. The ESIMS of **1** showed an $[M + H]^+$ ion at *m*/*z* 467, and HRESIMS measurements gave the molecular formula $C_{19}H_{21}N_2O_2{}^{79}Br_2$ + H. The ^1H and ^{13}C NMR data of **1** were similar to those reported by Goh and coworkers.[2c] The 6*β*,7*β*-dibromo configuration of **13** was assigned by analogy to leuconoxine and its congeners, where H or OH substituents attached to C-7 in the diazaspiro leuconoxine skeleton has to be *β*-oriented (7*α*-substituted analogues are highly strained, and none are known). In addition, the observed NOE between H-6 and H-9 is only possible if H-6 is *α*-oriented.

The bromination of alkenes is a well-known reaction, which usually yields *trans*-dibromo products as a consequence of *anti*-addition of bromine. The generally accepted mechanism invokes the intermediacy of a bromonium ion intermediate. In this instance however, a *cis*-dibromo addition product was clearly obtained as the sole product. Deviations from *trans* selectivity, usually giving rise to *cis*/*trans* mixtures of addition products, have been observed, e.g., in acenaphthylene.[21] Deviations from *trans* selectivity are explained by the intermediacy of nonbridged cationic species such as the *β*-bromocarbocation[22] or more recently by the intermediacy of the tribromide adduct.[23]

The exclusive formation of a *cis*-dibromo addition product **13** may be explained by acid-catalyzed epimerization of the *trans* addition product (formed with exclusive *trans* selectivity via the bromonium ion) or from *cis*/*trans* mixtures formed via the intermediacy of the *β*-bromocarbocation or the tribromide adduct.

It was at first envisaged that a hydroboration reaction on 6,7-dehydroleuconoxine (**10**) might lead to 6-hydroxyleuconoxine (or leuconodine A, **14**), a new leuconoxine-type alkaloid from *L. griffithii*.[9] However, when **10** was treated with $BH_3{\cdot}SMe_2$ (5 equiv) in THF at room temperature,[24] a complex mixture of products was obtained from which two leuconoxine-type derivatives arising from reduction of the C-2 lactam carbonyl, viz., **15** (completely reduced product, 37%) and **16** (partially reduced product, 6%), were isolated.

Compound **15** was obtained as a yellowish oil and subsequently as yellowish needles from MeOH (mp 128−132 °C), with $[\alpha]^{25}_D$ = +584 (*c* 0.4, $CHCl_3$). The UV spectrum showed absorption maxima at 209, 246, and 388 nm, while the IR spectrum showed a conjugated lactam carbonyl at 1641 and 1682 cm^{-1}. The ESIMS of **15** showed an $[M + H]^+$ ion at *m*/*z* 295, in agreement with the molecular formula $C_{19}H_{22}N_2O$ + H. A notable difference in the ^1H NMR spectrum of **15** when compared with that of 6,7-dehydroleuconoxine (**10**) was the presence of two additional proton resonances due to a methylene group adjacent to a heteroatom at δ_H 3.55 and 3.81, attributable to H-2 (based on HMQC). Also, the characteristic C-2 lactam carbonyl resonance observed in the ^{13}C NMR spectrum of **15** was replaced by a resonance at δ_C 40.8 attributed to C-2 in **15**. These observations indicated deoxygenation at C-2 of **15**. Compound **15** is therefore 2-dihydro-6,7-dehydroleuconoxine.

Compound **16** was obtained as a fluorescent yellowish oil and subsequently as fluorescent yellowish rods (mp 198−200 °C), with $[\alpha]^{25}_D$ = +667 (*c* 0.3, $CHCl_3$). The UV spectrum showed absorption maxima at 209, 245, and 394 nm, while the IR spectrum showed an OH band at 3343 cm^{-1} and a conjugated lactam carbonyl at 1666 cm^{-1}. The ESIMS of **16** showed an $[M + H]^+$ ion at *m*/*z* 311, in agreement with the molecular formula $C_{19}H_{22}N_2O_2$ + H. Notable differences in the ^1H NMR spectrum of **16** when compared with that of 6,7-dehydroleuconoxine (**10**) were the presence of a low-field proton resonance at δ_H 5.52 due to H-2 and a broad OH resonance at δ_H 4.02. The ^{13}C NMR spectrum showed the absence of the characteristic C-2 lactam resonance, while displaying an additional resonance at δ_C 76.1, attributed to C-2. These observations indicated that the C-2 carbonyl in **16** has been reduced to an OH. The C-2 configuration was assigned as *S*, based on the observed NOE between C-2 and C-12. Compound **16** is therefore 2*α*-hydroxy-6,7-dehydroleuconoxine.[25] The structures of **15** and **16** were both confirmed by X-ray diffraction analysis (Figure 5).

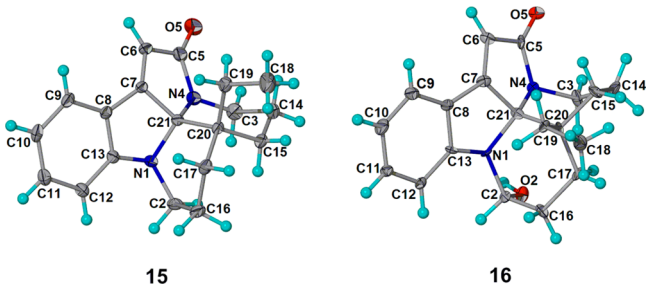

Figure 5. X-ray crystal structures of **15** and **16**.

Since hydroboration of **10** did not furnish leuconodine A (**14**), a direct *α*-oxygenation of leuconoxine (**3**) at C-6, via enolate-mediated oxidation, was next attempted. However, treatment of leuconoxine (**3**) with lithium diisopropylamide (LDA) in THF at 0 °C, followed by oxidation of the lactam enolate with O_2,[27] gave compound **17** as the sole product (21%), accompanied by a significant amount of unreacted **3** (69%). The enolate-mediated oxidation occurred at C-16 instead of at C-6, possibly due to the formation of the more stable six-membered enolate.

Compound **17** was obtained as a colorless oil and subsequently as colorless needles from CH_2Cl_2/hexanes (mp

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184−186) with $[\alpha]^{25}_D$ = −29 (*c* 0.2, $CHCl_3$). The UV spectrum showed absorption maxima at 210, 241, and 374 nm, while the IR spectrum showed the presence of an OH (3417 cm^{-1}) and carbonyl functions (1691 cm^{-1}, broad). The ESIMS of **17** showed an $[M + H]^+$ ion at *m/z* 327, in agreement with the molecular formula $C_{19}H_{22}N_2O_3$ + H. Notable differences in the ^1H NMR spectrum of **17** when compared with that of **3** include the downfield shift of H-16 from δ_H 2.78 and 2.49 in **3** to δ_H 4.45 in **17** and the presence of an OH resonance at δ_H 3.28 (exchangeable with D_2O) in **17**. The ^{13}C NMR data showed that the resonance due to C-16 had shifted downfield (δ_C 64.9) when compared with that of **3**. These results strongly suggested that oxidation had occurred at C-16. The relative configuration at C-16 was assigned as *R*, based on the observed NOE between H-16 and H-15*α*. Compound **17** is therefore 16*β*-hydroxyleuconoxine. Suitable crystals of **17** were obtained from CH_2Cl_2/hexanes, and an X-ray diffraction analysis confirmed the structure assignment (Figure 6).

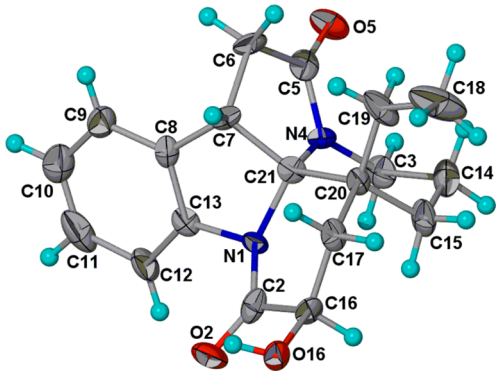

Figure 6. X-ray crystal structure of **17**.

Leuconodine A (**14**) was eventually obtained by treatment of leuconolam (**1**) with excess trifluoroacetic acid (TFA). Treatment of leuconolam (**1**) with TFA (2 equiv) resulted in transannular cyclization to 6,7-dehydroleuconoxine (**10**) via the iminium ion **9**. The use of excess TFA (20 equiv) gave a mixture of two products, viz., **10** (30% yield) and leuconodine A (**14**) (25% yield).

The formation of **14** and **10** in the presence of excess TFA is rationalized in Scheme 3. The possibility that conjugate addition by the TFA anion to the conjugated iminium ion **9** competes with transannular cyclization to **10**, leading eventually to leuconodine A (**14**) (Scheme 3, path a), is rendered less likely on account of the poor nucleophilicity of the trifluoromethylacetate anion. A preferred pathway is via a [3,3] sigmatropic shift (analogous to the Overman rearrangement of allylic trichloroacetimidates)[28] from the ester **19**, formed by the reaction of **1** with excess TFA (Scheme 3, path b). This pathway would also account for the stereoselectivity observed (6*β*-OH). Subsequently, Dess−Martin periodinane (DMP) oxidation of leuconodine A (**14**) afforded the new leuconoxine alkaloid leuconodine F (**19**).[9,29]

CONCLUSION

Several transformations of the ring-opened *Aspidosperma* alkaloid leuconolam (**1**) were investigated. The based-induced reaction of leuconolam (**1**) resulted in enolate-mediated transannular cyclization to give two epimeric pentacyclic meloscine-like products, **6** and **7**, while the acid-induced reactions (HCl in two-phase medium, CSA in CH_2Cl_2) resulted in transannular cyclization to give 6,7-dehydroleuconoxine (**10**). A two-step sequence from leuconolam (**1**), comprising acid-induced cyclization, followed by catalytic hydrogenation, provided a concise semisynthesis of leuconoxine (**3**). When the acid-induced reaction of leuconolam (**1**) or 6,7-dehydroleuconoxine (**10**) was carried out with PTSA in CH_2Cl_2, the product was the amino lactam-lactone **11**, while the acid-induced reactions in MeOH afforded *O*-methylleuconolam (**8**) as the sole product in high yields. The original assignment of the structure of *epi*-leuconolam (**2**) was revised to 6,7-dehydroleuconoxine (**10**) based on X-ray diffraction analysis, which was prompted by inconsistencies observed in the various transformations of leuconolam and its supposed C-21 epimer, "*epi*-leuconolam". Bromination (Br_2/$CHCl_3$) of leuconolam (**1**) proceeds in two steps via intermediacy of 6,7-dehydroleuconoxine (**10**) to furnish the 6*β*,7*β*-dibromoleuconoxine adduct (**13**). Concise semisyntheses of the new leuconoxine-type alkaloids leuconodines A (**14**) and F (**19**) were achieved by transformation of leuconolam (**1**) with excess TFA into leuconodine A (**14**) and **10** and subsequently by oxidation of **14** to leuconodine F (**19**).

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were measured on a Mel-Temp melting point apparatus and were uncorrected. Optical rotations were recorded on a JASCO P-1020 digital polarimeter. IR spectra were recorded on a Perkin-Elmer Spectrum 400 spectrophotometer or on a Perkin-Elmer 1600 Series FT-IR spectrophotometer. UV spectra were obtained on a Shimadzu UV-3101PC spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a JEOL JNM-LA 400, JNM-ECA 400, or Bruker Avance III 400 spectrometer, at 400 and 100 MHz, respectively, or on a Bruker Avance III 600 spectrometer at 600 and 150 MHz, respectively. ESIMS and HRESIMS were obtained on an Agilent 6530 Q-TOF mass spectrometer. EIMS and HREIMS were obtained at Organic Mass Spectrometry, Central Science Laboratory, University of Tasmania, Tasmania, Australia. All air/moisture-sensitive reactions were carried out under N_2 in oven-dried glassware. THF was freshly distilled from Na/benzophenone under N_2, MeOH was freshly distilled from Mg turnings under N_2, and CH_2Cl_2 was distilled from CaH_2 under N_2. All other reagents were used without further purification.

Source of Compounds 1 and 10. Compounds **1** and **10** were previously isolated from *Leuconotis griffithii*.[9]

*Leuconolam (**1**):* colorless block crystals from MeOH; mp 178−180 °C [lit.[2] 263−264 °C]; $[\alpha]^{25}_D$ −303 (*c* 0.8, $CHCl_3$) [lit.[2] $[\alpha]_D$ −28.3 (*c* 0.7 $CHCl_3$)]; UV (EtOH) λ_{max} (log ε) 205 (4.00), 220 (3.22), and 292 (3.96) nm; IR (dry film) ν_{max} 3263, 1683, and 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.55 (1H, t, *J* = 7.5 Hz, H-18), 1.23 (1H, dq, *J* = 13.6, 7.5 Hz, H-19b), 1.40 (1H, br t, *J* = 14.5 Hz, H-17b), 1.48 (2H, m, H-14a, H-14b), 1.57 (1H, m, H-15b), 1.60 (1H, td, *J* = 14.5, 7.3 Hz, H-17a), 1.60 (1H, m, H-19a), 1.79 (1H, td, *J* = 13.5, 4.5 Hz, H-15a), 1.99 (1H, td, *J* = 14, 1.7 Hz, H-16b), 2.12 (1H, dd, *J* = 14, 7.3 Hz, H-16a), 2.94 (1H, td, *J* = 12.5, 4.5 Hz, H-3b), 3.98 (1H, dd, *J* = 12.5, 4.5 Hz, H-3a), 4.99 (1H, br s, 21-OH), 5.77 (1H, s, H-6), 7.18 (1H, dd, *J* = 7.5, 1.5 Hz, H-9), 7.33 (1H, td, *J* = 7.5, 1.5 Hz, H-11), 7.36 (1H, td, *J* = 7.5, 1.5 Hz, H-10), 7.71(1H, br s, *NH*), 7.91 (1H, td, *J* = 7.5, 1.5 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.9 (CH, C-18), 19.7 (CH_2, C-14), 24.5 (CH_2, C-15), 25.4 (CH_2, C-17), 27.3 (CH_2, C-19), 32.1 (CH_2, C-16), 35.3 (CH_2, C-3), 44.9 (C, C-20), 93.6 (C, C-21), 126.3 (CH, C-10), 126.6 (CH, C-12), 128.1 (CH, C-6), 129.3 (CH, C-9), 129.4 (CH, C-11), 133.1 (C, C-8), 135.0 (C, C-13), 155.6 (C, C-7), 166.5 (C, C-5), 177.8 (C, C-2); ESIMS *m/z* 327 $[M + H]^+$ ($C_{19}H_{22}N_2O_3$ + H).

*6,7-Dehydroleuconoxine (**10**) (formerly epi-leuconolam):* colorless block crystals from CH_2Cl_2/hexanes; mp 164−168 °C; $[\alpha]^{25}_D$

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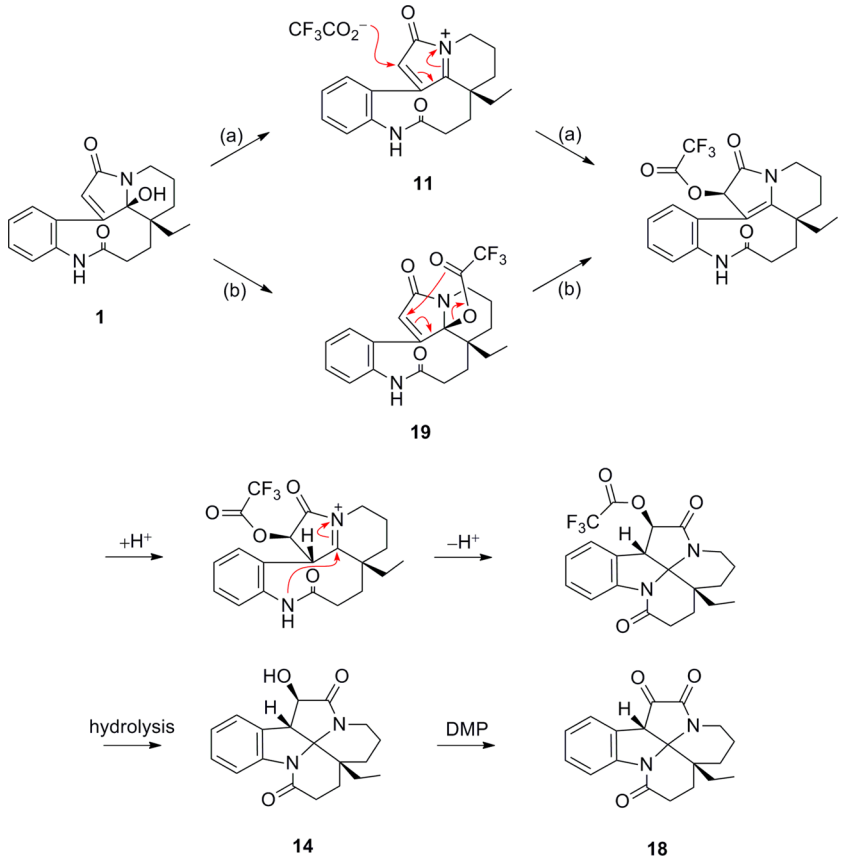
Scheme 3. Formation of 14 and 18



+271 (*c* 0.1, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 203 (4.32), 252 (4.33), and 350 (3.70) nm; IR (dry film) ν_{max} 1691, 1649, and 1595 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.76 (1H, t, *J* = 7.4 Hz, H-18), 1.10 (1H, td, *J* = 14, 7 Hz, H-15b), 1.35 (1H, dq, *J* = 13.6, 7.4 Hz, H-19b), 1.45 (1H, dq, *J* = 13.6, 7.4 Hz, H-19a), 1.66 (1H, ddd, *J* = 14, 6, 1.5 Hz, H-15a), 1.71 (1H, td, *J* = 15, 5 Hz, H-17b), 1.79 (1H, m, H-14b), 2.04 (1H, m, H-14a), 2.09 (1H, ddd, *J* = 15, 6, 2 Hz, H-17a), 2.62 (1H, *J* = 15, 5, 2 Hz, H-16b), 3.09 (1H, td, *J* = 15, 6 Hz, H-16a), 3.22 (1H, ddd, *J* = 15, 9.6, 6 Hz, H-3b), 4.46 (1H, ddd, *J* = 15, 12, 4 Hz, H-3a), 6.22 (1H, s, H-6), 7.12 (1H, td, *J* = 7.5, 1 Hz, H-10), 7.33 (1H, td, *J* = 7.5, 1 Hz, H-11), 7.46 (1H, ddd, *J* = 7.5, 1, 0.6 Hz, H-9), 8.16 (1H, ddd, *J* = 7.5, 1, 0.6 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.3 (CH, C-18), 16.8 (CH_2, C-14), 26.0 (CH_2, C-15), 30.4 (CH_2, C-17), 33.1 (CH_2, C-16), 34.1 (CH_2, C-19), 37.0 (CH_2, C-3), 44.6 (C, C-20), 93.7 (C, C-21), 115.9 (CH, C-12), 118.2 (CH, C-6), 121.6 (CH, C-9), 123.5 (C, C-8), 124.3 (CH, C-10), 131.6 (CH, C-11), 148.6 (C, C-13), 164.2 (C, C-7), 173.5 (C, C-5), 176.1 (C, C-2); ESIMS *m*/*z* 309 $[M + H]^+$; HRESIMS *m*/*z* 309.1590 $[M + H]^+$ (calcd for $C_{19}H_{20}N_2O_2$ + H, 309.1598).

Reaction of Leuconolam (1) with KOH, MeOH/EtOH. Leuconolam (**1**) (50 mg, 0.15 mmol) was dissolved in methanolic ethanol (9:1, 50 mL). Two pellets of KOH were added, and the solution was stirred at rt for 6 h, quenched with 5% HCl (20 mL), and basified with 10% $NaHCO_3$ (30 mL). The mixture was extracted with CH_2Cl_2 (4 × 100 mL), washed with H_2O, dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 10% MeOH/Et_2O, NH_3-saturated) to give **5** (6 mg, 12%) and **7** (1.5 mg, 3%) and recovered **1** (10 mg, 20%).

Compound ***6:*** colorless oil and subsequently as colorless block crystals from CCl_4/MeOH; mp 266−268 °C [lit.[2c] 175−177 °C]; $[\alpha]^{25}_D$ −198 (*c* 0.06, $CHCl_3$) [lit.[2c] $[\alpha]_D$ −14.3 (*c* 0.35, $CHCl_3$)]; UV (EtOH) λ_{max} (log ε) 210 (4.50), 253 (4.01), and 287 (3.38) nm; IR (dry film) ν_{max} 3226 and 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.67 (1H, t, *J* = 7.6 Hz, H-18), 0.96 (1H, dq, *J* = 14, 7.6 Hz, H-19b), 1.08 (1H, dq, *J* = 14, 7.6 Hz, H-19a), 1.44 (1H, m, H-15b), 1.59 (2H, m, H-14a, H-14b), 1.81 (1H, dt *J* = 14.5, 4.5 Hz, H-15a), 2.20 (1H, ddd, *J* = 14, 10.5, 2 Hz, H-17b), 2.32 (1H, dd, *J* = 14, 2.5 Hz, H-17a), 2.38 (1H, br s, 21-OH), 2.69 (1H, d, *J* = 17.7 Hz, H-6*β*), 2.91 (1H, m, H-16), 2.94 (1H, m, H-3b), 3.03 (1H, d, *J* = 17.7 Hz, H-6*α*), 4.23 (1H, dt, *J* = 13, 7.5 Hz, H-3a), 6.76 (1H, dd, *J* = 8, 1.5 Hz, H-12), 7.10 (1H, td, *J* = 8, 1.5 Hz, H-11), 7.23 (1H, td, *J* = 8, 1.5 Hz, H-10), 7.39 (1H, dd, *J* = 8, 1.5 Hz, H-9), 8.41 (1H, br s, *NH*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.4 (CH, C-18), 19.6 (CH, C-14), 26.3 (CH_2, C-19), 28.0 (CH_2, C-15), 32.2 (CH_2, C-17), 37.2 (CH_2, C-3), 46.7 (C, C-20), 50.0 (CH_2, C-6), 50.6 (C, C-8), 51.9 (CH, C-16), 100.8 (C, C-21), 116.1 (CH, C-12), 122.0 (C, C-8), 123.8 (CH, C-10), 129.0 (CH, C-11), 129.1 (CH, C-9), 136.0 (C, C-13), 170.5 (C, C-2), 171.0 (C, C-5); ESIMS *m*/*z* 327 $[M + H]^+$; HRESIMS *m*/*z* 327.1712 $[M + H]^+$ (calcd for $C_{19}H_{22}N_2O_3$ + H, 327.1703).

Compound ***7:*** colorless oil and subsequently as colorless block crystals from MeOH; mp 250−252 °C; $[\alpha]^{25}_D$ −150 (*c* 0.01, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.46), 251 (4.22), and 306 (3.00) nm; IR (dry film) ν_{max} 3322, 1712, and 1681 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (1H, t, *J* = 7.3 Hz, H-18), 1.20 (1H, td, *J* = 14.5, 6.8 Hz, H-15b), 1.41 (1H, m, H-19b), 1.56 (1H, m, H-17b), 1.59 (1H, m, H-19a), 1.66 (2H, m, H-14a, H-14b), 1.82 (1H, dt, *J* = 14.5, 4.5 Hz, H-15a),2.17 (1H, dd, *J* = 13.7, 5 Hz, H-17a), 2.35 (1H, d, *J* = 18 Hz, H-6*β*), 2.75 (1H, d, *J* = 18 Hz, H-6*α*), 2.90 (1H, br s, 21-OH), 3.07 (1H, dd, *J* = 13.7, 5.5 Hz, H-16), 3.08 (1H, m, H-3b), 4.03 (1H, dt, *J* = 13, 7.5 Hz, H-3a), 6.85 (1H, br d, *J* = 7.8 Hz, H-9), 7.01 (1H, td, *J* = 7.8, 1.5 Hz, H-11), 7.19 (1H, td, *J* = 7.8, 1.5 Hz, H-10), 7.69 (1H, d, *J* = 7.8 Hz, H-12), 7.65 (1H, br s, *NH*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.8 (CH, C-18), 24.0 (CH_2, C-19), 30.0 (CH_2, C-15), 30.4 (CH_2, C-17), 36.6 (CH_2, C-3), 41.5 (CH_2, C-6), 46.3 (CH, C-16), 50.0 (C, C-7), 50.3 (C, C-20), 99.2 (C, C-21), 117.0 (CH, C-12), 123.6 (CH, C-10), 123.9 (CH, C-9), 127.9 (CH, C-11), 133.0 (C, C-8), 137.2 (C, C-13), 170.7 (C, C-2), 171.1 (C, C-5); ESIMS *m*/*z* 327 $[M + H]^+$;

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HRESIMS m/z 327.1710 $[M + H]^+$ (calcd for $C_{19}H_{22}N_2O_3$ + H, 327.1703).

Reaction of Leuconolam (1) with 5% HCl. To a stirred solution of 5% HCl (5 mL) was added **1** (11 mg, 0.034 mmol). The mixture was stirred for 12 h at rt, quenched with 10% Na_2CO_3 (10 mL), extracted with CH_2Cl_2 (3 × 10 mL), washed with H_2O (3 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. TLC of the residue showed only the presence of **1** (8.9 mg, 81% recovery).

Reaction of Leuconolam (1) with 5% HCl/CH_2Cl_2 in the Presence of Tetraethylammonium Chloride. Leuconolam (**1**) (14.5 mg, 0.044 mmol) was added to a two-phase system comprising 5% HCl (5 mL), CH_2Cl_2 (5 mL), and TEACl (7 mg, 0.044 mmol). The mixture was stirred for 12 h at rt, quenched with 10% Na_2CO_3 (10 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with H_2O (3 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/Et_2O, NH_3-saturated) to give 6,7-dehydroleuconoxine (**10**) (6.5 mg, 47%), amino lactam-lactone **11** (0.2 mg, 1.4%), and recovered **1** (5.1 mg, 35%).

*Amino Lactam-lactone **11**:* yellowish oil and subsequently as yellowish block crystals from CH_2Cl_2/hexanes; mp 179−182 °C; $[\alpha]^{25}_D$ +116 (*c* 0.5, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 212 (4.87), 240 (4.83), and 342 (4.01) nm; IR (dry film) ν_{max} 3483, 3397, 1743, and 1709 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.68 (1H, t, J = 87.6 Hz, H-18), 1.26 (1H, m, H-19b), 1.28 (1H, m, H-17b), 1.43 (1H, m, H-15b), 1.45 (1H, m, H-17a), 1.51 (1H, m, H-19a), 1.53 (1H, m, H-15a), 1.58 (1H, m, H-14), 2.20 (1H, ddd, J = 19, 10, 1.2 Hz, H-16b), 2.44 (1H, ddd, J = 19, 6, 1.5 Hz, H-16a), 2.82 (1H, ddd, J = 13, 4, 2 Hz, H-3b), 3.94 (2H, br s, NH_2), 4.09 (1H, ddd, J = 13, 11, 4 Hz, H-3a), 6.14 (1H, s, H-6), 6.65 (1H, td, J = 8, 1.5 Hz, H-10), 6.65 (1H, dd, J = 8, 1.5 Hz, H-12), 6.96 (1H, dd, J = 8, 1.5 Hz, H-9), 7.09 (1H, td, J = 8, 1.5 Hz, H-11); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 7.1 (CH, C-18), 19.8 (CH, C-14), 25.0 (CH_2, C-19), 25.5 (CH_2, C-15), 25.6 (CH_2, C-17), 26.3 (CH_2, C-16), 35.9 (CH_2, C-3), 37.9 (C, C-20), 102.1 (C, C-21), 116.6 (CH, C-12), 118.0 (C, C-8), 118.4 (CH, C-10), 121.9 (CH, C-6), 128.9 (CH, C-9), 130.8 (CH, C-11), 144.1 (C, C-13), 155.7 (C, C-7), 166.8 (C, C-5), 170.6 (C, C-2); EIMS m/z (rel int) 326 $[M]^+$ (100), 299 (5), 280 (10), 267 (12), 239 (20), 225 (5), 209 (7), and 185 (8); HREIMS m/z $[M]^+$ 326.1629 (calcd for $C_{19}H_{22}N_2O_3$, 326.1630).

Reaction of Leuconolam (1) with Concentrated HCl in MeOH. Leuconolam (**1**) (12.9 mg, 0.040 mmol) was dissolved in a minimal amount of MeOH (ca. 0.1 mL). Concentrated HCl (2 drops) was added dropwise. The mixture was stirred for 16 h at rt, quenched with 10% Na_2CO_3 (10 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with H_2O (3 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/Et_2O, NH_3-saturated) to give *O*-methylleuconolam (**8**) (8.6 mg, 63%) and recovered **1** (0.5 mg, 4%).

*O-Methylleuconolam (**8**):* colorless oil and subsequently as colorless block crystals from MeOH; mp 214−218 °C [lit.[2] 155−156 °C]; $[\alpha]^{25}_D$ −240 (*c* 0.6, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 238 (3.99) and 348 (3.03) nm; IR (dry film) ν_{max} 3477 and 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.55 (1H, t, J = 7.5 Hz, H-18), 1.28 (1H, dq, J = 13.6, 7.5 Hz, H-19b), 1.49 (2H, m, H-14a, H-14b), 1.50 (3H, m, H-15b, H-16b, H-17b), 1.54 (1H, m, H-19a), 1.75 (1H, m, H-17a), 2.05 (1H, ddd, J = 15, 5, 2 Hz, H-15a), 2.17 (1H, td, J = 15, 6 Hz, H-16a), 2.61 (1H, td, J = 12.5, 4 Hz, H-3b), 3.15 (3H, s, 21-OMe), 4.18 (1H, td, J = 12.5, 4 Hz, H-3a), 6.33 (1H, s, H-6), 7.26 (1H, ddd, J = 7.5, 1, 0.5 Hz, H-9), 7.34 (1H, m, H-10), 7.41 (1H, m, H-11), 7.42 (1H, m, H-12), 8.25 (1H, br s, *NH*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.3 (CH, C-18), 19.6 (CH_2, C-14), 24.1 (CH_2, C-19), 26.2 (CH_2, C-17), 28.0 (CH_2, C-16), 32.5 (CH_2, C-15), 35.9 (CH_2, C-3), 45.5 (C, C-20), 49.9 (CH_3, 21-O*Me*), 97.4 (C, C-21), 126.7 (CH, C-9), 127.0 (CH, C-10), 128.6 (CH, C-12), 129.9 (CH, C-11), 131.9 (CH, C-6), 133.1 (C, C-8), 135.7 (C, C-13), 151.0 (C, C-7), 166.8 (C, C-5), 178.6 (C, C-2); ESIMS m/z 341 $[M + H]^+$ ($C_{20}H_{24}N_2O_3$ + H).

Reaction of Leuconolam (1) with 10-Camphorsulfonic Acid in Anhydrous CH_2Cl_2. To a stirred solution of CSA (15 mg, 0.066 mmol) and CH_2Cl_2 (5 mL) was added leuconolam (**1**) (14.3 mg, 0.044 mmol). The mixture was stirred for 12 h at rt, quenched with 10% K_2CO_3 (10 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/Et_2O, NH_3-saturated) to give 6,7-dehydroleuconoxine (**10**) (8.2 mg, 62%), amino lactam-lactone **11** (0.1 mg, 2%), and recovered **1** (1.4 mg, 10%).

Reaction of Leuconolam (1) with CSA in Anhydrous CH_2Cl_2/MeOH. To a stirred solution of CSA (13.2 mg, 0.057 mmol) and CH_2Cl_2 (5 mL) was added leuconolam (**1**) (11.8 mg, 0.038 mmol). The mixture was stirred for 30 min, and MeOH (6 μL, 0.152 mmol) was added. The mixture was stirred for another 11 h at rt, quenched with 10% K_2CO_3 (10 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extract was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/Et_2O, NH_3-saturated) to give *O*-methylleuconolam (**8**) (6.6 mg, 54%) and 6,7-dehydroleuconoxine (**10**) (2.2 mg, 19%).

Reaction of Leuconolam (1) with CSA in Anhydrous MeOH. To a stirred solution of CSA (11.8 mg, 0.051 mmol) and MeOH (5 mL) was added leuconolam (**1**) (11 mg, 0.034 mmol). The mixture was stirred for 12 h at rt, quenched with 10% K_2CO_3 (10 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extract was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/Et_2O, NH_3-saturated) to give *O*-methylleuconolam (**8**) (10.9 mg, 94%), amino lactam-lactone **11** (0.1 mg, 2%), and recovered **1** (0.4 mg, 4%).

Reaction of Leuconolam (1) with *p*-Toluenesulfonic Acid in Anhydrous MeOH. To a stirred solultion of PTSA (9.5 mg, 0.056 mmol) and MeOH (5 mL) was added leuconolam (**1**) (12 mg, 0.037 mmol). The mixture was stirred for 12 h at rt, quenched with 10% K_2CO_3 (10 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extract was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/Et_2O, NH_3-saturated) to give *O*-methylleuconolam (**8**) (11.8 mg, 94%), amino lactam-lactone **11** (0.1 mg, 0.8%), and recovered **1** (0.4 mg, 4%).

Reaction of Leuconolam (1) with PTSA in Anhydrous CH_2Cl_2. To a stirred solution of PTSA (8.6 mg, 0.05 mmol) and CH_2Cl_2 (5 mL) was added leuconolam (**1**) (11.7 mg, 0.036 mmol). The mixture was stirred for 15 h at rt, quenched with 10% Na_2CO_3 (10 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, Et_2O, NH_3-saturated) to give 6,7-dehydroleuconoxine (**10**) (0.6 mg, 5%), amino lactam-lactone **11** (5 mg, 42%), and recovered **1** (0.4 mg, 3%).

Reaction of 6,7-Dehydroleuconoxine (10) with 5% HCl/CH_2Cl_2 in the Presence of TEACl. 6,7-Dehydroleuconoxine (**10**) (19.5 mg, 0.063 mmol) was added into a two-phase system comprising 5% HCl (5 mL), CH_2Cl_2 (5 mL), and TEACl (10 mg, 0.063 mmol). The mixture was stirred for 12 h at rt, quenched with 10% Na_2CO_3 (10 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with H_2O (3 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/Et_2O, NH_3-saturated) to give leuconolam (**1**) (2.9 mg, 15%) and recovered 6,7-dehydroleuconoxine (**10**) (16.3 mg, 84%).

Reaction of 6,7-Dehydroleuconoxine (10) with CSA in Anhydrous CH_2Cl_2. To a stirred solution of CSA (11.8 mg, 0.051 mmol) and CH_2Cl_2 (5 mL) was added 6,7-dehydroleuconoxine (**10**) (11 mg, 0.034 mmol). TLC of the reaction mixture after 15 h showed traces of leuconolam (**1**) and amino lactam-lactone **11**, in addition to the starting material **10**.

Reaction of 6,7-Dehydroleuconoxine (10) with PTSA in Anhydrous CH_2Cl_2. To a stirred solution of PTSA (9.2 mg, 0.054 mmol) and CH_2Cl_2 (5 mL) was added 6,7-dehydroleuconoxine (**10**) (10.3 mg, 0.036 mmol). The mixture was stirred for 10 h at rt,

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quenched with 10% Na_2CO_3 (10 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, Et_2O, NH_3-saturated) to give amino lactam-lactone **11** (7.1 mg, 70%) and recovered **10** (0.3 mg, 1%).

Reaction of *O*-Methylleuconolam (8) with PTSA in Anhydrous CH_2Cl_2. To a stirred solution of PTSA (8 mg, 0.044 mmol) and CH_2Cl_2 (5 mL) was added *O*-methylleuconolam (**8**) (10 mg, 0.029 mmol). TLC of the mixture after 10 h showed traces of leuconolam (**1**) and amino lactam-lactone (**11**), in addition to the starting material **8**.

Hydrogenation of Leuconolam (1). Leuconolam (**1**) (20 mg, 0.061 mmol) was dissolved in CH_2Cl_2 (5 mL) and stirred over 10% Pd/C (12.4 mg) under a hydrogen atmosphere at rt. TLC of the mixture every 1 h for 6 h showed only the presence of the stating material, **1**.

Hydrogenation of 6,7-Dehydroleuconoxine (10). 6,7-Dehydroleuconoxine (**10**) (20 mg, 0.061 mmol) was dissolved in CH_2Cl_2 (5 mL) and stirred over 10% Pd/C (12.4 mg) under a hydrogen atmosphere at rt for 1 h. The catalyst was removed by filtration over Celite. Evaporation of the solvent *in vacuo*, followed by chromatography of the resulting residue (SiO_2, 5% MeOH/Et_2O, NH_3-saturated), gave leuconoxine (**3**) (18.1 mg, 90%) as a colorless oil and subsequently as colorless block crystals from MeOH; mp 210−215 °C (lit.[3] 238−242 °C); $[\alpha]^{25}_D$ −86 (*c* 0.7, $CHCl_3$) [lit.[3] $[\alpha]^{25}_D$ −88 (*c* 1.2, MeOH)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (1H, t, *J* = 7.4 Hz, H-18), 1.37 (1H, dq, *J* = 13.4, 7.4 Hz, H-19b), 1.60 (4H, m, H-14a, H-14b, H-15b), 1.78 (1H, dq, *J* = 13.4, 7.4 Hz, H-19a), 1.86 (1H, ddd, *J* = 14, 6.5, 1.4 Hz, H-17b), 1.97 (1H, ddd, *J* = 14, 12, 5 Hz, H-15a, H-17a), 2.49 (1H, ddd, *J* = 19, 6, 1.4 Hz, H-16b), 2.68 (1H, d, *J* = 17 Hz, H-6b), 2.78 (1H, ddd, *J* = 19, 14, 6.5 Hz, H-16a), 2.80 (1H, m, H-3b), 2.87 (1H, dd, *J* = 17, 7.3 Hz, H-6a), 3.82 (1H, d, *J* = 7.3 Hz, H-7), 3.95 (1H, ddt, *J* = 13, 4.4, 2.3 Hz, H-3a), 7.14 (1H, td, *J* = 7.6, 1 Hz, H-10), 7.17 (1H, dd, *J* = 7.6, 1 Hz, H-9), 7.25 (1H, td, *J* = 7.6, 1 Hz, H-11), 7.77 (1H, dd, *J* = 7.6, 1 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.3 (CH, C-18), 20.1 (CH_2, C-14), 26.2 (CH_2, C-15), 26.6 (CH_2, C-17), 26.9 (CH_2, C-19), 29.4 (CH_2, C-16), 36.8 (CH_2, C-3), 37.6 (CH_2, C-6), 38.1 (C, C-20), 41.9 (CH, C-7), 92.5 (C, C-21), 120.1 (CH, C-12), 123.8 (CH, C-9), 125.5 (CH, C-10), 128.0 (CH, C-11), 135.4 (C, C-8), 142.1 (C, C-13), 170.8 (C, C-5), 172.9 (C, C-2); ESIMS *m*/*z* 311 $[M + H]^+$ ($C_{19}H_{22}N_2O_2$ + H).

Bromination of Leuconolam (1). Leuconolam (**1**) (11 mg, 0.034 mmol) was dissolved in $CHCl_3$ (4 mL), and Br_2 (2.6 μL, 0.051 mmol) was added dropwise at rt. After being stirred for 14 h, the mixture was quenched with 10% $NaHSO_3$ or Na_2CO_3 (10 mL), extracted with $CHCl_3$ (3 × 5 mL), washed with H_2O, and dried (Na_2SO_4), the solvent removed *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/$CHCl_3$, NH_3-saturated) to give 6*β*,7*β*-dibromoleuconoxine (**13**) (13.7 mg, 86%) as a white, amorphous solid; $[\alpha]^{25}_D$ −38 (*c* 0.62, $CHCl_3$) [lit.[2] $[\alpha]^{25}_D$ −32 (*c* 0.5, $CHCl_3$)]; UV (EtOH) λ_{max} (log ε) 208 (4.32), 227 (4.22), and 292 (3.35) nm; IR (dry film) ν_{max} 1709 and 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (1H, t, *J* = 7 Hz, H-18), 1.56 (1H, m, H-14b), 1.60 (1H, m, H-14a), 1.62 (1H, m, H-15b), 1.73 (1H, m, H-19b), 1.98 (1H, m, H-19a), 2.03 (1H, m, H-17b), 2.23 (1H, m, H-17a), 2.64 (1H, m, H-16b), 2.73 (1H, m, H-3b), 2.75 (1H, m, H-15a), 2.82 (1H, m, H-16a), 4.08 (1H, ddd, *J* = 13.5, 4, 2 Hz, H-3a), 5.17 (1H, s, H-6), 7.24 (1H, dt, *J* = 7.2, 1 Hz, H-10), 7.33 (1H, m, H-9), 7.36 (1H,m, H-11), 7.80 (1H, dd, *J* = 7.2, 1 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.0 (CH, C-18), 19.6 (CH_2, C-14), 24.5 (CH_2, C-15), 25.5 (CH_2, C-17), 28.0 (CH_2, C-19), 29.4 (CH_2, C-16), 38.7 (CH_2, C-3), 39.2 (C, C-20), 50.6 (CH, C-6), 63.7 (C, C-7), 100.5 (C, C-21), 120.9 (CH, C-12), 123.8 (CH, C-10), 126.5 (CH, C-9), 130.4 (CH, C-11), 136.9 (C, C-8), 139.2 (C, C-13), 164.3 (C, C-5), 172.4 (C, C-2); ESIMS *m*/*z* 467 $[M + H]^+$.

Bromination of 6,7-Dehydroleuconoxine (10). 6,7-Dehydroleuconoxine (**10**) (7 mg, 0.021 mmol) was dissolved in $CHCl_3$ (4 mL), Br_2 (1.2 μL, 0.032 mmol) was added dropwise at rt, and the mixture was stirred for 13 h. The mixture was quenched with 10% Na_2CO_3 (10 mL), extracted with $CHCl_3$ (3 × 5 mL), washed with H_2O, and dried (Na_2SO_4), the solvent removed *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/$CHCl_3$, NH_3-saturated) to give 6*β*,7*β*-dibromoleuconoxine (**13**) (9.6 mg, 96%).

Debromination of 6*β*,7*β*-Dibromoleuconoxine (13). To a solution of 6*β*,7*β*-dibromoleuconoxine (**13**) (13 mg, 0.028 mmol) in HOAc (5 mL) was added freshly activated Zn (91 mg, 0.139 mmol). The mixture was stirred for 2 h, after which the mixture was poured into saturated Na_2CO_3 (30 mL), extracted with CH_2Cl_2 (3 × 20 mL), washed with H_2O (3 × 20 mL), and dried (Na_2SO_4), the solvent removed *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/$CHCl_3$, NH_3-saturated) to give 6,7-dehydroleuconoxine (**10**) (3.7 mg, 41%).

Reaction of 6,7-Dehydroleuconoxine (10) with BH_3·SMe_2. BH_3·SMe_2 (75 μL, 1 M in THF) was added to 6,7-dehydroleuconoxine (**10**) (16 mg, 0.051 mmol) in THF (5 mL), and the mixture was stirred for 24 h at rt. The progress of the reaction was monitored by TLC, and the reaction was quenched with NH_4Cl solution when >95% of the starting material had been consumed. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), washed with H_2O (3 × 20 mL), dried over Na_2SO_4, and filtered, the solvent removed *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/$CHCl_3$, NH_3-saturated) to give compounds **15** (5.6 mg, 37%) and **16** (1 mg, 6%).

*Compound **15**:* yellowish oil and subsequently as yellowish needles from MeOH; mp 128−132 °C; $[\alpha]^{25}_D$ +584 (*c* 0.4, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (3.65), 246 (3.86), and 388 (3.02) nm; IR (dry film) ν_{max} 1682 and 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (1H, t, *J* = 7.6 Hz, H-18), 1.14 (1H, dq, *J* = 13.2, 7.6 Hz, H-19b), 1.15 (1H, m, H-17b), 1.38 (1H, dq, *J* = 13.2, 7.6 Hz, H-19a), 1.53 (1H, m, H-17a), 1.56 (2H, m, H-14a, H-14b), 1.69 (2H, m, H-15b, H-16b), 2.00 (2H, m, H-15a, H-16a), 3.05 (1H, ddd, *J* = 13.5, 4.5, 2 Hz, H-3b), 3.55 (1H, ddd, *J* = 15.4, 11, 7.8 Hz, H-2b), 3.81 (1H, dd, *J* = 15.4, 7.8 Hz, H-2a), 4.31 (1H, ddd, *J* = 13, 11, 4.5 Hz, H-3a), 6.16 (1H, s, H-6), 6.75 (1H, dd, *J* = 7.5, 1 Hz, H-12), 6.83 (1H, td, *J* = 7.5, 1 Hz, H-10), 7.24 (1H, td, *J* = 7.5, 1 Hz, H-11), 7.36 (1H, dd, *J* = 7.5, 1 Hz, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.3 (CH, C-18), 17.0 (CH_2, C-16), 20.1 (CH_2, C-14), 25.4 (CH_2, C-17), 27.4 (CH_2, C-15), 29.6 (CH_2, C-19), 39.0 (CH_2, C-3), 40.8 (CH_2, C-2), 41.4 (C, C-20), 94.5 (C, C-21), 109.7 (CH, C-12), 116.9 (CH, C-6), 119.7 (CH, C-10), 122.4 (CH, C-9), 122.5 (C, C-8), 131.3 (CH, C-11), 157.0 (C, C-13), 166.1 (C, C-7), 173.7 (C, C-5); ESIMS *m*/*z* 295 $[M + H]^+$; HRESIMS *m*/*z* $[M + H]^+$ 295.1792 (calcd for $C_{19}H_{22}N_2O$ + H, 295.1805).

*Compound **16**:* fluorescent yellowish oil and subsequently as fluorescent yellowish rods from CH_2Cl_2/hexanes; mp 198−200 °C; $[\alpha]^{25}_D$ +667 (*c* 0.3, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (4.14), 245 (4.42), and 394 (3.64) nm; IR (dry film) ν_{max} 3343, 1666, and 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.55 (1H, t, *J* = 7.4 Hz, H-18), 0.87 (1H, m, H-15b), 0.97 (1H, dq, *J* = 13.1, 7.4 Hz, H-19b), 1.27 (1H, dq, *J* = 13.1, 7.4 Hz, H-19a), 1.31 (1H, m, H-17b), 1.54 (1H, m, H-14b), 1.73 (2H, m, H-15a, H-16b), 1.81 (1H, m, H-16a), 1.84 (1H, m, H-14a), 3.67 (1H, ddd, *J* = 14, 4, 2 Hz, H-3b), 3.99 (1H, ddd, *J* = 14, 11, 4 Hz, H-3a), 4.02 (1H, br s, OH), 5.52 (1H, br s, H-2), 5.67 (1H, s, H-6), 6.60 (1H, br d, *J* = 8.2 Hz, H-12), 6.68 (1H, br t, *J* = 7.8 Hz, H-10), 6.99 (1H, dd, *J* = 7.8, 1 Hz, H-9), 7.15 (1H, td, *J* = 8.2, 1 Hz, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.3 (CH, C-18), 18.1 (CH_2, C-14), 21.5 (CH_2, C-17), 23.8 (CH_2, C-16), 24.0 (CH_2, C-15), 29.6 (CH_2, C-19), 35.8 (CH_2, C-3), 42.3 (C, C-20), 76.1 (CH, C-2), 94.7 (C, C-21), 108.2 (CH, C-12), 117.3 (CH, C-6), 119.3 (CH, C-10), 120.0 (C, C-8), 122.7 (CH, C-9), 131.3 (CH, C-11), 153.7 (C, C-13), 166.1 (C, C-7), 177.1 (C, C-5); ESIMS *m*/*z* 311 $[M + H]^+$; HRESIMS *m*/*z* $[M + H]^+$ 311.1750 (calcd for $C_{19}H_{22}N_2O_2$ + H, 311.1754).

Attempted Enolate-Mediated C-6 Oxidation of Leuconoxine (3). A solution of **3** (11 mg, 0.035 mmol) in THF (5 mL) was added to a solution of LDA (27 μL, 2 M in THF) in THF (10 mL) at 0 °C, and the resulting mixture was stirred for 30 min. Dry O_2 was bubbled into the solution for 10 min. A Na_2SO_3 solution (1 M, 2 mL) was

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added, and the mixture extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified by centrifugal preparative TLC (SiO_2, 5% MeOH/Et_2O, NH_3-saturated) to afford compound **17** (2.4 mg, 21%) and recovered **3** (7.6 mg, 69%).

Compound 17: colorless oil and subsequently as colorless needles from CH_2Cl_2/hexanes; mp 184−186 °C; $[\alpha]^{25}_D$ −29 (*c* 0.2, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.10), 241 (3.88), and 274 (3.23) nm; IR (dry film) ν_{max} 3417 and 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (1H, t, *J* = 7.3 Hz, H-18), 1.38 (1H, de, *J* = 14.5, 7.1 Hz, H-19b), 1.50 (1H, m, H-17b), 1.51 (1H, m, H-14b), 1.56 (1H, m, H-14a), 1.66 (2H, m, H-15b, H-19a), 1.82 (1H, ddd, *J* = 14.5, 11, 4 Hz, H-15a), 2.26 (1H, dd, *J* = 13, 6 Hz, H-17a), 2.56 (1H, d, *J* = 17 Hz, H-6b), 2.69 (1H, ddd, *J* = 13.5, 4.5, 1.5 Hz, H-3b), 2.77 (1H, dd, *J* = 17, 7.8 Hz, H-6a), 3.81 (1H, m, H-3a), 3.83 (1H, d, *J* = 7.8 Hz, H-7), 4.45 (1H, dd, *J* = 13, 6 Hz, H-16), 7.13 (1H, m, H-10), 7.21 (1H, m, H-11), 7.22 (1H, m, H-9), 7.60 (1H, br d, *J* = 7.8 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.5 (CH, C-18), 20.0 (CH_2, C-14), 28.1 (CH_2, C-15), 29.3 (CH_2, C-19), 35.9 (CH_2, C-17), 36.8 (CH_2, C-3), 37.4 (CH_2, C-6), 38.9 (C, C-20), 42.4 (CH, C-7), 64.9 (CH, C-16), 93.7 (C, C-21), 120.9 (CH, C-12), 124.0 (CH, C-9), 126.3 (CH, C-10), 128.0 (CH, C-11), 135.3 (C, C-8), 140.9 (C, C-13), 171.0 (C, C-5), 175.0 (C, C-2); ESIMS *m/z* 327 $[M + H]^+$; HRESIMS *m/z* $[M + H]^+$ 327.1710 (calcd for $C_{19}H_{22}N_2O_3$ + H, 327.1703).

Reaction of Leuconolam (1) with Trifluoroacetic Acid. To a stirred solution of **1** (11 mg, 0.034 mmol) and CH_2Cl_2 (5 mL) was added TFA (9.5 μL, 0.068 mmol). The mixture was stirred for 13 h at rt, quenched with 10% Na_2CO_3 (10 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/Et_2O, NH_3-saturated) to give 6,7-dehydroleuconoxine (**2**) (4.1 mg, 37%) and recovered leuconolam (**1**) (5.8 mg, 53%).

Reaction of Leuconolam (1) with Excess Trifluoroacetic Acid. To a stirred solution of **1** (13 mg, 0.04 mmol) and CH_2Cl_2 (5 mL) was added TFA (60 μL, 0.8 mmol). The mixture was stirred for 12 h at rt, quenched with 10% Na_2CO_3 (10 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*, and the residue purified by centrifugal preparative TLC (SiO_2, 5% MeOH/Et_2O, NH_3-saturated) to 6,7-dehydroleuconoxine (**2**) (3.9 mg, 30%), leuconodine A (**14**) (3.3 mg, 25%), and recovered **1** (1.2 mg, 9%).

Leuconodine A (14): colorless oil and subsequently as colorless block crystals from EtOH; mp 134−136 °C (lit.[9] 135−138 °C); $[\alpha]^{25}_D$ −18 (*c* 0.03, $CHCl_3$) (lit.[9] −20 (*c* 0.26, $CHCl_3$)); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (1H, t, *J* = 7.3 Hz, H-18), 1.49 (1H, dq, *J* = 13, 7.3 Hz, H-19b), 1.60 (1H, m, H-17b), 1.64 (1H, m, H-15b), 1.70 (2H, m, H-14a, H-14b), 1.92 (1H, m, H-15a), 1.94 (1H, m, H-17a), 1.96 (1H, m, H-19a), 2.53 (1H, ddd, *J* = 19, 6, 1.4 Hz, H-16b), 2.78 (1H, ddd, *J* = 19, 14, 6.5 Hz, H-16a), 2.89 (1H, ddd, *J* = 13, 11, 4 Hz, H-3b), 3.90 (1H, s, H-7), 3.99 (1H, ddd, *J* = 13, 5, 2 Hz, H-3a), 4.51 (1H, s, H-6), 7.13 (1H, td, *J* = 7.8, 1 Hz, H-10), 7.25 (1H, td, *J* = 7.8, 1 Hz, H-11), 7.27 (1H, dd, *J* = 7.8, 1 Hz, H-9), 7.87 (1H, dd, *J* = 7.8, 1 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.7 (CH, C-18), 19.4 (CH_2, C-14), 27.3 (CH_2, C-15), 27.5 (CH_2, C-17), 28.5 (CH_2, C-19), 30.2 (CH_2, C-16), 36.7 (C, C-20), 36.8 (CH_2, C-3), 49.6 (CH, C-7), 75.1 (CH, C-6), 93.5 (C, C-21), 119.6 (CH, C-12), 124.5 (CH, C-9), 125.4 (CH, C-10), 128.3 (CH, C-11), 132.1 (C, C-8), 141.9 (C, C-13), 172.0 (C, C-5), 173.1 (C, C-2); ESIMS *m/z* $[M + H]^+$ 327.

Oxidation of Leuconodine A (14). A solution of **14** (7 mg, 0.021 mmol) in CH_2Cl_2 (5 mL) was treated with the Dess−Martin periodinane (82 μL, 0.3 M in CH_2Cl_2), and the mixture was stirred at rt for 30 min. Et_2O (25 mL) and NaOH (10 mL, 1.3 M) were added, and the mixture was stirred for another 15 min. The aqueous layer was removed, the organic layer was washed with 1.3 M NaOH (2 × 10 mL) and dried with Na_2SO_4, the solvent was removed *in vacuo*, and the residue was purified by centrifugal preparative TLC (SiO_2, 5% MeOH/Et_2O, NH_3-saturated) to give leuconodine F (**19**) (5.3 mg, 76%) as a colorless oil and subsequently as colorless block crystals from MeOH: mp 246−250 °C; $[\alpha]^{25}_D$ +94 (*c* 0.05, $CHCl_3$) (lit.[29] +75 (*c* 0.03, $CHCl_3$)); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (1H, t, *J* = 7.4 Hz, H-18), 1.23 (1H, dq, *J* = 13, 7.4 Hz, H-19b), 1.49 (1H, dq, *J* = 13, 7.4 Hz, H-19a), 1.66 (1H, td, *J* = 14, 6 Hz, H-17b), 1.71 (3H, m, H-14a, H-14b, H-15b), 1.98 (1H, ddd, *J* = 14, 6.5, 1.4 Hz, H-17a), 2.05 (1H, m, H-15a), 2.59 (1H, ddd, *J* = 19, 6, 1.4 Hz, H-16b), 2.86 (1H, ddd, *J* = 19, 14, 6.5 Hz, H-16a), 3.10 (1H, ddd, *J* = 13, 11, 4 Hz, H-3b), 4.11 (1H, ddt, *J* = 13, 5, 2.3 Hz, H-3a), 4.23 (1H, s, H-7), 7.16 (1H, td, *J* = 7.6, 1 Hz, H-10), 7.22 (1H, dd, *J* = 7.6, 1 Hz, H-9), 7.37 (1H, td, *J* = 7.6, 1 Hz, H-11), 7.82 (1H, dd, *J* = 7.6, 1 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.3 (CH, C-18), 20.1 (CH_2, C-14), 26.3 (CH_2, C-15), 26.6 (CH_2, C-17), 27.7 (CH_2, C-19), 29.5 (CH_2, C-16), 37.6 (C, C-20), 37.8 (CH_2, C-3), 53.4 (CH, C-7), 88.0 (C, C-21), 121.0 (CH, C-12), 125.1 (CH, C-9), 125.9 (CH, C-10), 126.2 (C, C-8), 129.9 (CH, C-11), 142.6 (C, C-13), 157.5 (C, C-5), 172.2 (C, C-2), 192.5 (C, C-6); ESIMS *m/z* $[M + H]^+$ 325.

X-ray Crystallographic Analysis of 1, 6, 7, 10, 11, 15, 16, and 17. X-ray diffraction analysis was carried out on a Bruker SMART APEX II CCD area detector system equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (λ = 0.71073 Å), at 100 or 298 K. The structure was solved by direct methods (SHELXS-97) and refined with full-matrix least-squares on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were placed in idealized positions and refined as riding atoms with relative isotropic parameters. Crystallographic data for compounds **1**, **6**, **7**, **10**, **11**, **15**, **16**, and **17** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223-336033, or e-mail: deposit@ccdc.cam.ac.uk).

Crystallographic data of 1: colorless block crystals, $C_{19}H_{22}N_2O_3 \cdot CH_3OH$, M_r = 358.43, orthorhombic, space group $P2_12_12_1$, *a* = 8.1771(1) Å, *b* = 10.8938(2) Å, *c* = 19.8901(3) Å, *V* = 1771.80(5) $Å^3$, *T* = 100 K, *Z* = 4, D_{calcd} = 1.344 g cm^{-3}, crystal size 0.25 × 0.32 × 0.43 mm^3, *F*(000) = 768.0. The final R_1 value is 0.0310 (wR_2 = 0.0891) for 3896 reflections [$I > 2\sigma(I)$]. CCDC number: 970038.

Crystallographic data of 6: colorless block crystals, $2C_{19}H_{22}N_2O_3 \cdot 3H_2O$, M_r = 704.80, triclinic, space group *P*1, *a* = 10.1848(2) Å, *b* = 10.3620(2) Å, *c* = 10.3848(2) Å, α = 71.7420(10)°, β = 67.3780(10)°, γ = 60.6470(10)°, *V* = 871.11(3) $Å^3$, *T* = 100 K, *Z* = 2, D_{calcd} = 1.344 g cm^{-3}, crystal size 0.10 × 0.21 × 0.6102 mm^3, *F*(000) = 376.0. The final R_1 value is 0.0562 (wR_2 = 0.1185) for 6370 reflections [$I > 2\sigma(I)$]. CCDC number: 970039.

Crystallographic data of 7: colorless block crystals, $C_{19}H_{22}N_2O_3$, M_r = 326.39, orthorhombic, space group $P2_12_12_1$, *a* = 9.6652(5) Å, *b* = 16.1799(9) Å, *c* = 21.1959(11) Å, *V* = 3314.7(3) $Å^3$, *T* = 100 K, *Z* = 8, D_{calcd} = 1.308 g cm^{-3}, crystal size 0.15 × 0.27 × 0.31 mm^3, *F*(000) = 1392.0. The final R_1 value is 0.0356 (wR_2 = 0.0877) for 4999 reflections [$I > 2\sigma(I)$]. CCDC number: 970040.

Crystallographic data of 10: colorless block crystals, $C_{19}H_{20}N_2O_2$, M_r = 308.37, orthorhombic, space group $P2_12_12_1$, *a* = 8.8855(4) Å, *b* = 11.3940(5) Å, *c* = 14.8635(7) Å, *V* = 1504.80 (12) $Å^3$, *T* = 100 K, *Z* = 4, D_{calcd} = 1.361 g cm^{-3}, crystal size 0.26 × 0.34 × 0.48 mm^3, *F*(000) = 656.0. The final R_1 value is 0.0374 (wR_2 = 0.0929) for 2316 reflections [$I > 2\sigma(I)$]. CCDC number: 970041.

Crystallographic data of 11: yellowish block crystals, $2C_{19}H_{22}N_2O_3 \cdot CH_2Cl_2$, M_r = 737.70, monoclinic, space group $P2_1$, *a* = 8.00860(10) Å, *b* = 14.9302(3) Å, *c* = 15.3044(3) Å, $\alpha = \gamma$, β = 94.6480(10)°, *V* = 1823.93(6) $Å^3$, *T* = 100 K, *Z* = 2, D_{calcd} = 1.447 gcm^{-3}, crystal size 0.04 × 0.17 × 0.63 mm^3, *F*(000) = 780.0. The final R_1 value is 0.0460 (wR_2 = 0.0998) for 10151 reflections [$I > 2\sigma(I)$]. CCDC number: 970042.

Crystallographic data of 15: yellowish needles, $C_{19}H_{22}N_2O$, M_r = 294.39, orthorhombic, space group $P2_12_12_1$, *a* = 11.2107(6) Å, *b* = 11.5443(6) Å, *c* = 12.1199(7) Å, *V* = 1568.55(15) $Å^3$, *T* = 100 K, *Z* = 4, D_{calcd} = 1.247 g cm^{-3}, crystal size 0.02 × 0.60 × 0.90 mm^3, *F*(000) = 632.0. The final R_1 value is 0.0379 (wR_2 = 0.0985) for 2057 reflections [$I > 2\sigma(I)$]. CCDC number: 970043.

Crystallographic data of 16: fluorescent yellowish rods, $C_{19}H_{24}N_2O_2$, M_r = 312.40, trigonal, space group $P3_1$, *a* = *b* = 11.4602(2) Å, *c* = 10.0616(2) Å, $\alpha = \beta$, γ = 120.00°, *V* = 1144.41(4)

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Å^3, T = 100 K, Z = 3, D_{calcd} = 1.351 g cm^{-3}, crystal size 0.20 × 0.20 × 0.70 mm^3, F(000) = 504.0. The final R_1 value is 0.1315 (wR_2 = 0.3669) for 3270 reflections [$I > 2\sigma(I)$]. CCDC number: 970044.

Crystallographic data of **17**: colorless needles, $C_{19}H_{22}N_2O_3$, M_r = 326.39, orthorhombic, space group $P2_12_12_1$, a = 7.1721(4) Å, b = 26.1619(13) Å, c = 27.9882(15) Å, V = 5251.6(5) Å^3, T = 298 K, Z = 12, D_{calcd} = 1.238 g cm^{-3}, crystal size 0.02 × 0.08 × 0.68 mm^3, F(000) = 2088.0. The final R_1 value is 0.0508 (wR_2 = 0.1153) for 3171 reflections [$I > 2\sigma(I)$]. CCDC number: 970045.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **1**, **3**, **6**−**8**, **10**−**11**, **13**−**17**, and **19**. X-ray crystallographic data in CIF format for compounds **1**, **6**, **7**, **10**, **11**, **15**, **16**, and **17**. This material 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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