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Asymmetric Syntheses of Nakinadine D, Nakinadine E, and Nakinadine F: Confirmation of Their Relative (*RS*,*SR*)-Configurations and Proposal of Their Absolute (2*S*,3*R*)-Configurations

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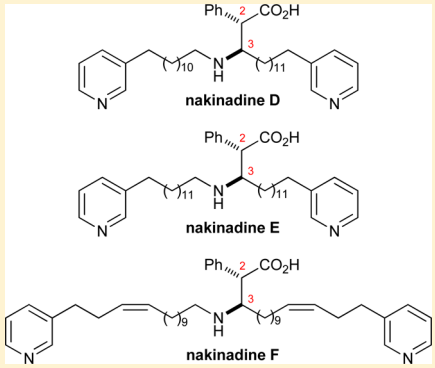
Supporting Information

ABSTRACT: The *syn*- and *anti*-diastereoisomeric forms of the reported structures of the marine alkaloids nakinadines D−F have been synthesized, for the first time in all cases, via an approach involving asymmetric Mannich-type (imino-aldol) reactions of methyl phenylacetate with *N*-*tert*-butylsulfinyl imines as the key steps to control the stereochemistry. Comparison of the ^{1}H and ^{13}C NMR spectroscopic data reported for the natural materials with those acquired for these synthetic samples confirms the initially assigned relative (*RS*,*SR*)-configurations of these three alkaloids. In the absence of specific rotation (or other diagnostic) data for the natural materials, it is not possible to unambiguously assign their absolute configurations, although given the absolute (2*S*)-configurations assigned to nakinadines B and C, and the absolute (2*S*,3*R*)-configuration previously established for nakinadine A, the data herein uphold our proposal that nakinadines D−F share the absolute (2*S*,3*R*)-configuration.



INTRODUCTION

The nakinadine alkaloids are a family comprising six members (nakinadines A−F) isolated by Kobayashi et al. in 2007 (nakinadine A)[1] and 2008 (nakinadines B−F).[2] At the heart of the structure of each of these alkaloids is an α-phenyl-β-amino acid moiety. A long chain *N*-alkyl substituent with a terminal 3-pyridyl moiety is also common to all the family members, but the presence of a similar substituent at the β-carbon atom within nakinadines A and D−F distinguishes them from nakinadines B and C (i.e., the former four possess a $\beta^{2,3}$-amino acid core, while the latter pair possess a β^{2}-amino acid core). Thus, for nakinadines A and D−F, there are four possible stereoisomeric forms (two enantiomeric pairs) with the further possibility for geometric isomerism in nakinadines A and F due to the presence of unsaturation in the long chain *N*- and/or C(β)-alkyl substituents. Kobayashi et al. assigned the absolute (*S*)-configurations to nakinadines B and C,[2] but only the relative (*RS*,*SR*)-configurations within nakinadines A and D−F were posited[1,2] and a specific rotation value was reported for nakinadine A only[1] (Figure 1).

To date, our asymmetric syntheses of nakinadines A−C are the only reported studies concerning any members of this alkaloid family:[3−5] we first developed syntheses of the most structurally simple members, nakinadines B[3] and C,[4] using the conjugate addition of lithium dibenzylamide to an enantiopure *N*-acryloyl SuperQuat derivative with *in situ* diastereoselective enolate protonation as the key step.[6,7] In this manner, the synthesis of nakinadine B was completed in 17% overall yield[3] and that of nakinadine C in 13% overall yield,[4] in nine steps in both cases from commercially available atropic acid.[3,4] In order to access the remaining family members, we envisaged the development of a common strategy based upon asymmetric Mannich-type (imino-aldol) reactions[8] using *N*-*tert*-butylsulfinylimines[9,10] (pioneered by Ellman et al.).[11] In this manner, it was anticipated that the syntheses of both the *syn*- and *anti*-diastereoisomers of each of nakinadines A and D−F (i.e., ignoring the possible geometric isomers of nakinadines A and F) would be achieved from only five readily available starting materials: enantiopure *N*-*tert*-butylsulfinylamide **1** (the source of chirality), methyl phenylacetate **2**, 12-(pyridin-3′-yl)-dodecanal **3**, 13-(pyridin-3′-yl)tridecanal **4**, and (*Z*)-14-(pyridin-3′-yl)tetradec-11-enal **5**. Of these, **1** and **2** are commercially available and **3**−**5** are readily prepared: in three steps from commercially available dodecane-1,12-diol for **4**,[3] and in two and five steps from commercially available 11-bromoundecan-1-ol for **3**[12] and **5**,[4,5] respectively. Condensation of **1** with either **4** or **5** would give the corresponding *N*-*tert*-butylsulfinylimines **6** and **7**. The key asymmetric imino-aldol reactions of **2** with either **6** or **7** would be followed by three-step sequences of *N*-deprotection, reductive *N*-alkylation (using **3**, **4**, or **5** as appropriate), and ester hydrolysis to deliver the target compounds (Figure 2). We have previously reported the syntheses of the *syn*- and *anti*-diastereoisomers of nakinadine A using this approach,[5] which enabled us to confirm the relative (*RS*,*SR*,*Z*)-configuration assigned to this alkaloid by Kobayashi et al.;[1] furthermore, through comparison of specific rotation values, we assigned the absolute (2*S*,3*R*,*Z*)-configuration to the natural product.[5] In this paper, we delineate our full results concerning the development of this methodology and its

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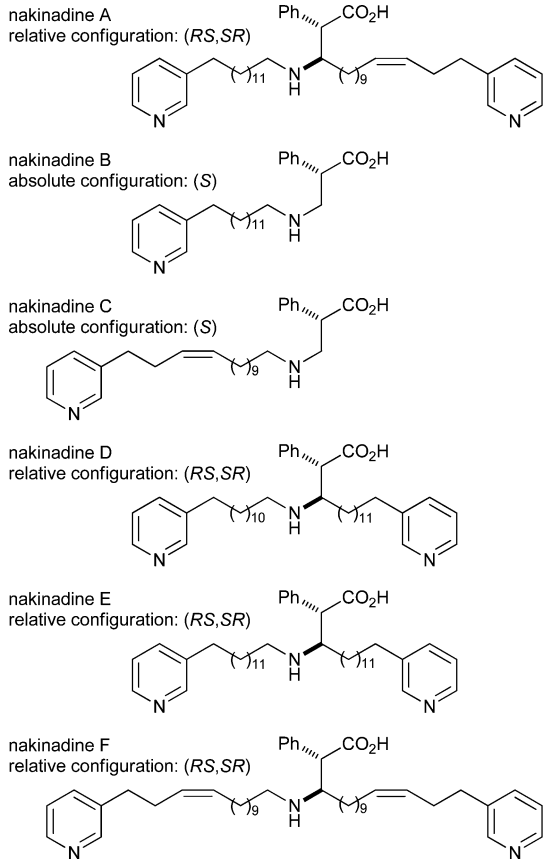


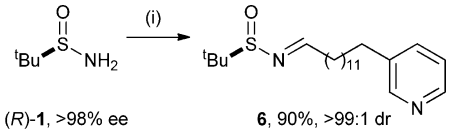
Figure 1. Structures and stereochemical assignments of the nakinadine alkaloids.

application to the syntheses of the *syn*- and *anti*-diastereoisomers of nakinadines D−F.

RESULTS AND DISCUSSION

Condensation of commercially available, enantiopure *tert*-butylsulfinamide (*R*)-**1** (>98% ee) with aldehyde **4**[3,13] in the presence of $MgSO_4$ and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS)[14] gave the saturated *N*-*tert*-butylsulfinylimine **6** in 90% yield as a single diastereoisomer (>99:1 dr), which was assigned the (*E*)-configuration by analogy to previous reports concerning this type of reaction[14] (Scheme 1).

Scheme 1[a]



[a]Reagents and conditions: (i) **4**, $MgSO_4$, PPTS, CH_2Cl_2, rt, 16 h.

Following the procedure outlined by Ellman et al.,[9] reaction of the titanium enolate of methyl phenylacetate **2** with **6** was initially investigated. Treatment of **2** (1.2 equiv) with LDA (1.3 equiv) at −78 °C was followed by sequential addition of $Ti(O^iPr)_3Cl$ (2.6 equiv) and then **6** (1.0 equiv). ^1H NMR spectroscopic analysis of the crude reaction mixture (in C_6D_6) after reaction for 3 h at −78 °C showed incomplete consumption of **6** (~37% conversion) to form two diastereoisomeric products in the ratio of 77:23. These were later unambiguously identified as **9** and **10**, respectively, following single crystal X-ray diffraction analysis of **9** and subsequent synthesis of authentic samples of all the possible diastereoisomeric products of this reaction (*vide infra*). The analogous reaction of the initially formed lithium enolate of **2** was also performed [i.e., omitting the addition of $Ti(O^iPr)_3Cl$] and resulted in the complete consumption of **6** to give a 56:38:6 ratio of diastereoisomers **9**, **10**, and **12**, respectively. Purification via flash column chromatography facilitated partial

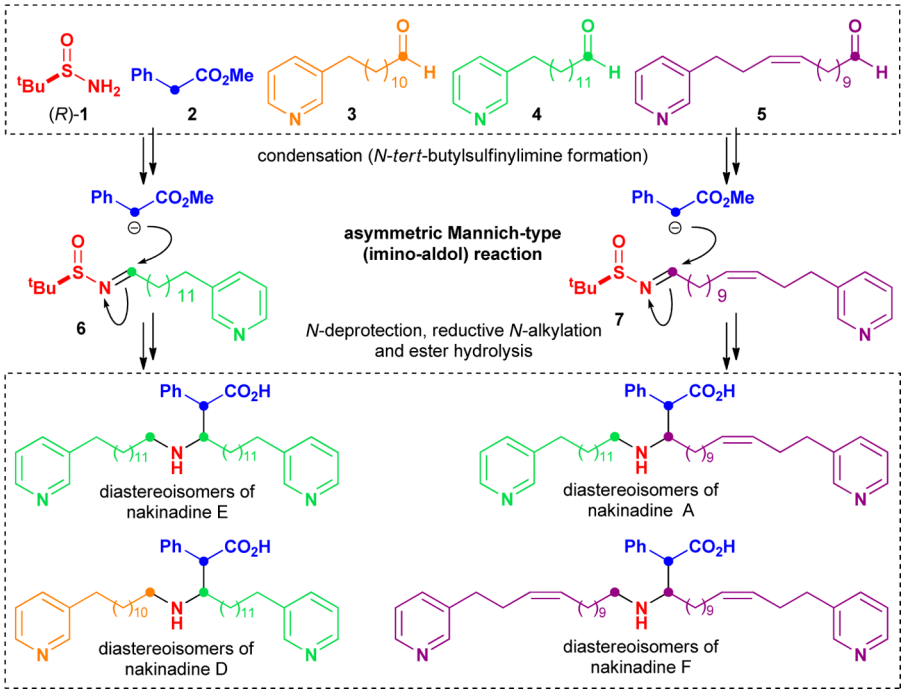


Figure 2. Proposed common strategy for the synthesis of the diastereoisomers of nakinadines A and D−F from the building blocks **1**−**5**.

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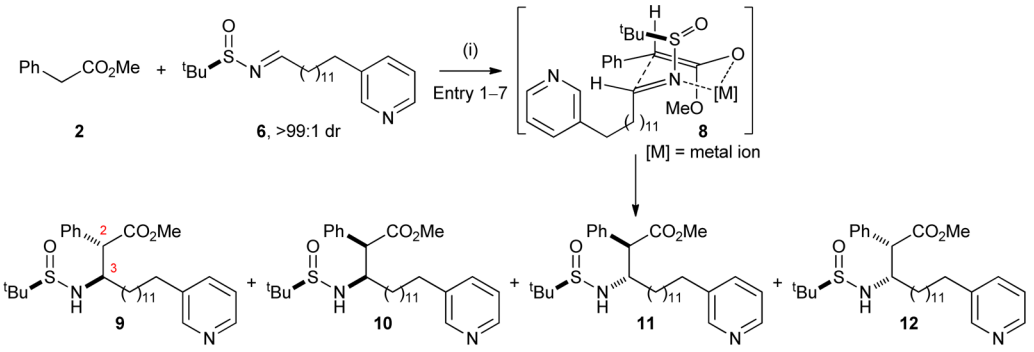
Scheme 2[a]



Entry	Base	Additive	Time	Conversion	Crude product ratio [9 : 10 : 11 : 12]	Isolated yield of 9 (diastereoisomeric purity)[b]	Isolated yield of 10 (diastereoisomeric purity)[b]
1[c]	LDA	$Ti(O^iPr)_3Cl$	3 h	37%	77 : 23 : 0 : 0	-	-
2[c]	LDA	none	3 h	quant	56 : 38 : 0 : 6	30% (93%)	20% (97%)
3[d]	LDA	LiCl	3 h	quant	76 : 22 : 0 : 2	50% (>99%)	10% (98%)
4	LiHMDS	LiCl	3 h	quant	82 : 15 : 1 : 2	42% (>99%)[e]	7% (98%)[e]
5	MeMgBr	none	3 h	42%	84 : 16 : 0 : 0	-	-
6	MeMgBr	$MgBr_2$	3 h	73%	86 : 14 : 0 : 0	-	-
7	MeMgBr	$MgBr_2$	6 h	quant	86 : 14 : 0 : 0	61% (>99%)	9% (98%)

[a]Reagents and conditions: (i) **2**, base, additive, THF, −78 °C, 30 min or 1 h, then **6**, −78 °C, 3 or 6 h (except for entry 1, where $Ti(O^iPr)_3Cl$ was added after 30 min and the resultant solution was allowed to stir for a further 45 min). 1.0 equiv of imine **6**, 1.2 equiv of methyl phenylacetate **2**, and 1.3 equiv of base were used (except for entries 5−7, which used 1.3 equiv of imine **6** and 1.2 equiv of MeMgBr). 5.0 equiv of additive was employed, where relevant (except for entry 1, which used 2.6 equiv of $Ti(O^iPr)_3Cl$). [b]Diastereoisomeric purity is the percentage of major diastereoisomer in the sample. [c]Reaction was conducted in the racemic series. [d]Reaction was conducted in both the racemic and the enantiopure series, and gave identical levels of diastereoselectivity in both cases; the isolated yields correspond to the enantiopure material. [e]A sample of **11** was also isolated from this reaction (<1% yield).

separation of this mixture, and **9**, **10**, and **12** were isolated in 50% combined yield. The inclusion of LiCl (5.0 equiv) had a beneficial effect on the diastereoselectivity of the reaction, giving a 76:22:2 mixture of **9**, **10**, and **12**, respectively. When LiHMDS was employed in place of LDA, the diastereoselectivity of the reaction increased further in favor of **9**: an 82:15:1:2 mixture of **9**, **10**, **11**, and **12**, respectively, was produced. Use of MeMgBr and $MgBr_2$ proved optimal and gave an 86:14 mixture of **9** and **10** (although 6 h was required for the reaction to reach full conversion). Purification via recrystallization led to the isolation of **9** in 61% yield and >99:1 dr. Exhaustive chromatography of the residue obtained from concentration of the mother liquor led to the isolation of **10** in 9% yield and 98:2 dr. The relative configuration within **9** was established unambiguously via single crystal X-ray diffraction analysis,[15] with its absolute (2*S*,3*R*,R_S)-configuration being assigned from the known (*R*)-configuration of the sulfur atom. The stereochemical outcome of the imino-aldol reaction is the combination of two distinct stereodefining steps: (i) the diastereoselectivity of the enolization of methyl phenylacetate **2** to give either the (*E*)- or (*Z*)-enolate, and (ii) the diastereofacial selectivities elicited upon addition of these enolates to imine **6**. The preponderance of the C(2)-epimeric products **9** and **10** in all the cases examined is consistent with very high selectivity for addition to the *Si* face of imine **6** (≥94:6 in all cases). For the reaction using LiHMDS, the (*E*):(*Z*) ratio of the intermediate lithium enolates was determined to be 90:10, respectively, in a separate enolate trapping experiment. The stereochemical outcome of the subsequent imino-aldol reaction (which forms **9** as the major product) is thus consistent with preferential reaction on the *Re* face at C(2) of the (*E*)-enolate and is, therefore, entirely in accord with transition state model **8**, initially proposed by Tang and Ellman to rationalize the diastereoselectivity of the reactions of titanium enolates in this reaction manifold.[9] The increase in diastereoselectivity of these reactions upon incorporation of a chelating additive adds further credence to this mechanistic postulate. Several attempts to trap the magnesium enolate(s) generated from treatment of **2** with MeMgBr consistently returned only starting material **2**, although the similar diastereoselectivities of the two imino-aldol reactions using LiHMDS/LiCl and MeMgBr/$MgBr_2$ suggest a similar ratio of the corresponding diastereoisomeric enolates (Scheme 2).

The identities of the other three possible diastereoisomeric products of this imino-aldol reaction (**10**−**12**) were unambiguously established by the synthesis of authentic samples from **9**. Epimerization of the C(2)-stereocenter within **9** was first investigated as it was envisaged that this would also provide a sample of the C(2)-epimeric compound for subsequent elaboration. Treatment of **9** with NaOMe in MeOH at 0 °C for 8 h gave a 20:80 mixture of **9** and **10**, respectively. Purification of this mixture via exhaustive flash column chromatography led to the isolation of **10** in 65% yield and 98:2 dr, thus establishing that **9** and **10** are epimeric at C(2), and so the absolute (2*R*,3*R*,R_S)-configuration within **10** was established unambiguously. When the crude reaction mixture from the imino-aldol reaction was subjected directly to these

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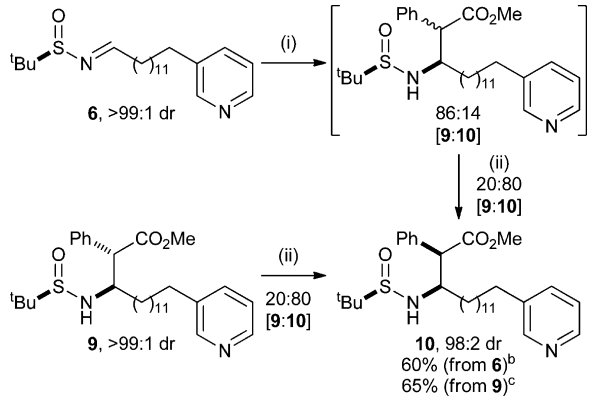
reaction conditions, the yield of **10** was 60% from **6** (Scheme 3).

Scheme 3[a]

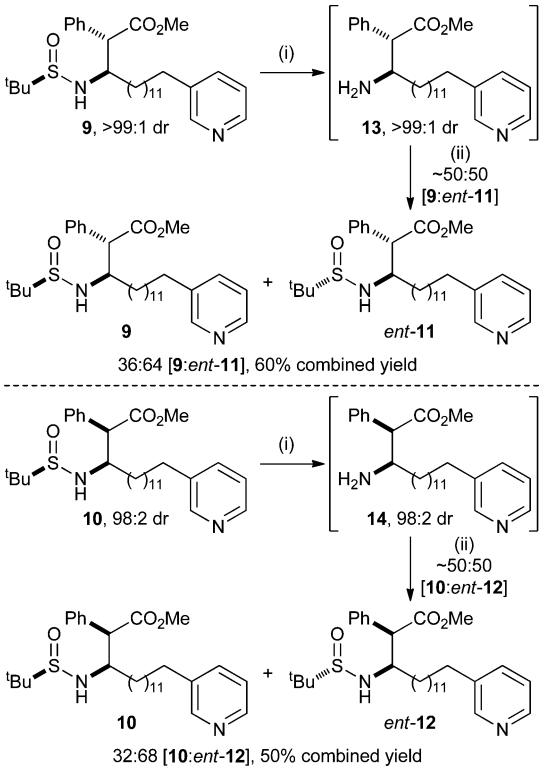


[a]Reagents and conditions: (i) **2**, MeMgBr, $MgBr_2$, THF, −78 °C, 1 h, then **6**, −78 °C, 6 h; (ii) NaOMe, MeOH, 0 °C, 8 h. [b]**9** was also isolated in 9% yield. [c]**9** was also isolated in 10% yield.

Removal of the *N*-*tert*-butylsulfinyl group from **9** (>99:1 dr) by treatment with HCl (1.25 M in MeOH)[9] resulted in the formation of **13**, and subsequent treatment of **13** with racemic *tert*-butylsulfinyl chloride (1.0 equiv) led to the formation of an ∼50:50 mixture of **9** and *ent*-**11**. Purification gave a 36:64 mixture of **9** and *ent*-**11** in 60% combined yield. Thus, the absolute (2*S*,3*R*,S_S)-configuration within *ent*-**11** could be assigned. Similarly, **10** (98:2 dr) was treated with HCl (1.25 M in MeOH)[9] to furnish **14**. Comparison of the ^{1}H NMR spectra of **13** and **14** confirmed that the hydrolysis step proceeded, in each case, without any competing epimerization. Subsequent reaction of **14** with racemic *tert*-butylsulfinyl chloride (1.0 equiv) gave an ∼50:50 mixture of **10** and *ent*-**12**. Purification gave a 32:68 mixture of **10** and *ent*-**12** in 50% combined yield, thus establishing the absolute (2*R*,3*R*,S_S)-configuration within *ent*-**12**. These correlation experiments allowed the absolute configurations within (2*R*,3*S*,R_S)-**11** and (2*S*,3*S*,R_S)-**12**, formed in the imino-aldol reaction, to be unambiguously assigned (Scheme 4).

With efficient routes to both **9** and **10** in hand, a strategy employing *N*-deprotection, reductive *N*-alkylation (with the requisite long chain aldehydes **3** and **4**), and ester hydrolysis was envisaged to complete the syntheses of the reported structures of nakinadines D and E and their C(2)-epimers. Thus, removal of the *N*-*tert*-butylsulfinyl group from **9** (>99:1 dr) using HCl (1.25 M in MeOH)[9] and treatment of **13** with either **3**[12,13] or **4**[3,13] in the presence of $NaB(OAc)_3H$ gave **15** and **16** in 63% and 62% yield (from **9**), respectively, and in >99:1 dr in both cases. Heating a solution of **15** in 3.0 M aq HCl at 100 °C for 8 h resulted in hydrolysis of the methyl ester. Purification of the crude reaction mixture via Amberlite CG-400 ion-exchange chromatography (100−200 mesh, OH^- form), followed by further purification via flash column chromatography on silica gel, gave **17** (possessing the reported relative configuration within nakinadine D)[2] in 60% yield and >99:1 dr. A similar experimental and purification procedure applied to **16** gave **18** (possessing the reported relative configuration within nakinadine E)[2] in 63% yield and >99:1 dr. The enantiomeric purities of **17**, **18**, and all intermediates were assigned as >98% ee based upon the enantiomeric purity

Scheme 4[a]



[a]Reagents and conditions: (i) HCl (1.25 M in MeOH), rt, 2 h, then satd aq $NaHCO_3$; (ii) (*RS*)-^{t}BuSOCl, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h.

of the *tert*-butylsulfinamide (*R*)-**1** (i.e., >98% ee). Therefore, these synthetic samples of nakinadine D **17** {$[\alpha]_D^{20}$ −15.0 (*c* 0.5 in $CHCl_3$)} and nakinadine E **18** {$[\alpha]_D^{20}$ −15.2 (*c* 0.5 in $CHCl_3$)} were synthesized in 15% and 16% overall yield, respectively, in eight steps (longest-linear sequence) from dodecane-1,12-diol in both cases. The C(2)-epimers of **17** and **18** were synthesized from **10** using an analogous approach. *N*-Deprotection of **10** (98:2 dr) using HCl (1.25 M in MeOH)[9] gave **14**, which was reductively *N*-alkylated using either **3**[12,13] or **4**[3,13] to furnish **19** or **20**, in 66% and 63% yield, respectively, and 98:2 dr in both cases. Comparison of the ^{1}H NMR spectra of **15** and **16** with the corresponding C(2)-epimers **19** and **20** confirmed that no epimerization had occurred during any of the reductive *N*-alkylation reactions. Hydrolysis of the methyl ester within **19** using HCl (3.0 M aq), followed by purification, gave **21** in 60% isolated yield, 98:2 dr, and >98% ee {$[\alpha]_D^{20}$ +8.0 (*c* 1.0 in $CHCl_3$)}. Similarly, treatment of **20** with HCl (3.0 M aq) gave **22** in 61% isolated yield, 98:2 dr, and >98% ee {$[\alpha]_D^{20}$ +8.4 (*c* 1.0 in $CHCl_3$)}. Therefore, these samples of **21** and **22** were synthesized in 16% and 15% overall yield, respectively, in nine steps (longest-linear sequences) from dodecane-1,12-diol in both cases (Scheme 5).

Attention next turned to the synthesis of nakinadine F. As previously described,[5] reaction of *N*-*tert*-butylsulfinamide (*R*)-**1** with aldehyde **5** [97:3 dr, (*E*):(*Z*) ratio][4,5,13] gave unsaturated *N*-*tert*-butylsulfinylimine **7** in 80% yield and 97:3 dr [(11*Z*):(11*E*) ratio].[5] Under the optimized conditions for imino-aldol reaction, addition of MeMgBr to a solution of methyl phenylacetate **2** and $MgBr_2$ in THF, followed by addition of imine **7**, furnished an ∼80:20 mixture of **23** and **24**, respectively. Purification via exhaustive flash column chromatography gave **23** in 60% yield and 97:3 dr [(*Z*):(*E*) ratio].[5,16]

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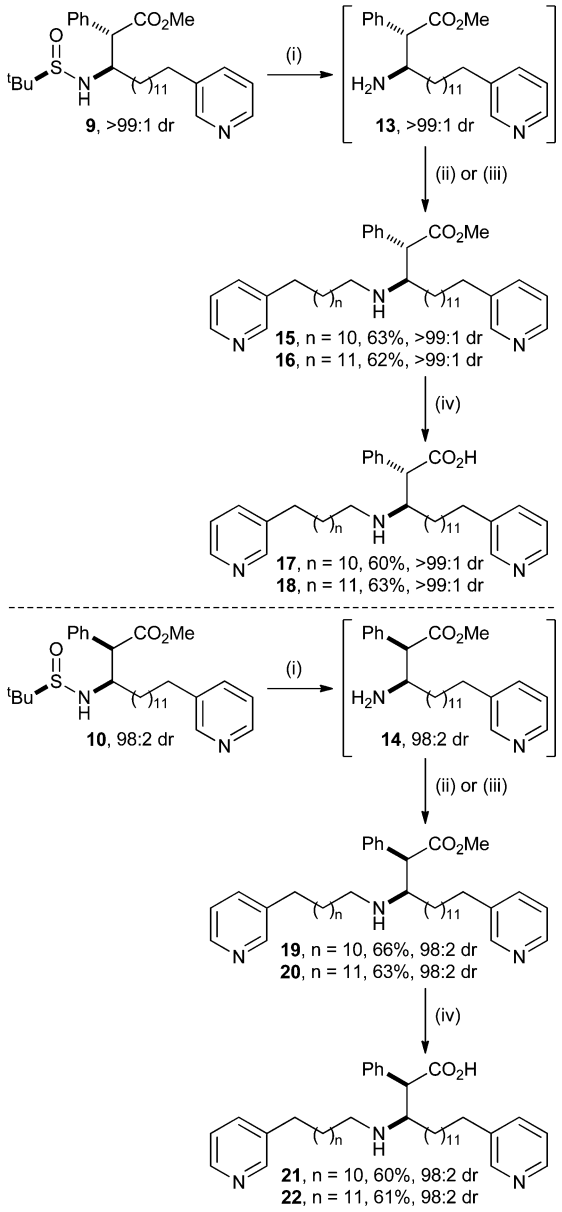
Scheme 5[a]

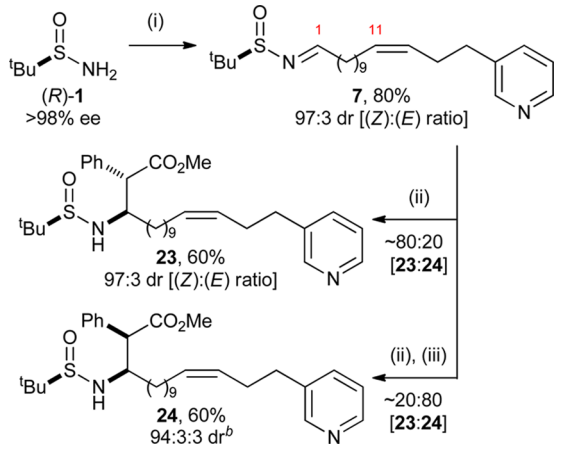


[a]Reagents and conditions: (i) HCl (1.25 M in MeOH), rt, 2 h, then satd aq $NaHCO_3$; (ii) **3**, $NaB(OAc)_3H$, AcOH, 1,2-dichloroethane, rt, 16 h; (iii) **4**, $NaB(OAc)_3H$, AcOH, 1,2-dichloroethane, rt, 16 h; (iv) HCl (3.0 M aq), 100 °C, 8 h.

Treatment of the crude reaction mixture from the imino-aldol reaction with NaOMe in MeOH at 0 °C gave an ~20:80 mixture of **23** and **24**, respectively, from which **24** was isolated in 60% yield and 94:3:3 dr [(2*R*,3*R*,R_S,*Z*):(2*R*,3*R*,R_S,*E*):(2*S*,3*R*,R_S,*Z*) ratio],[5,17] i.e., 94% diastereoisomeric purity[18] (Scheme 6).

Removal of the *N*-*tert*-butylsulfinyl group from **23** [97:3 dr, (*Z*):(*E*) ratio] via treatment with HCl (1.25 M in MeOH)[9] gave **25**, which was subsequently reductively *N*-alkylated using aldehyde **5** [97:3 dr, (*Z*):(*E*) ratio][4,5,13] to give **26** in 60% yield and ~95% diastereoisomeric purity.[18] Attempted hydrolysis of **26** using HCl (3.0 M aq) at 100 °C resulted in the formation of a complex mixture of products. Integration of peaks corresponding to the vinylic protons in the ^{1}H NMR spectrum of the crude reaction mixture showed that they had significantly

Scheme 6[a]



[a]Reagents and conditions: (i) **5** [97:3 dr, (*Z*):(*E*) ratio], $MgSO_4$, PPTS, CH_2Cl_2, rt, 16 h; (ii) **2**, MeMgBr, $MgBr_2$, THF, −78 °C, 30 min, then **7**, −78 °C, 6 h; (iii) NaOMe, MeOH, 0 °C, 8 h. [b]Ratio of the (2*R*,3*R*,R_S,*Z*)-, (2*R*,3*R*,R_S,*E*)-, and (2*S*,3*R*,R_S,*Z*)-diastereoisomers, respectively.

decreased in intensity as compared to the remainder of the signals, suggesting that the C=C bonds may have undergone side-reactions. Mass spectrometric analysis (ESI^+) of the crude reaction mixture showed peaks corresponding to the desired amino acid product **27** alongside peaks consistent with the presence of hydration products of one ($[M + 18]^+$) or both ($[M + 36]^+$) of the C=C double bonds. Attempted purification of the crude reaction mixture did not allow isolation of **27** in this case. When the temperature of the hydrolysis reaction was reduced to 70 °C, complete consumption of **26** occurred after 80 h with no evidence of competing hydration, and purification of the crude reaction mixture via Serdolit CG-400 I ion-exchange chromatography (100−200 mesh, OH^- form), followed by further purification via flash column chromatography, gave **27** (the reported stereostructure of nakinadine F)[2] in 56% yield, ~95% diastereoisomeric purity,[18] and >98% ee [based upon the enantiomeric purity of (*R*)-**1**]. Therefore, this synthetic sample of nakinadine F **27** {$[\alpha]_D^{20}$ −15.1 (*c* 1.0 in $CHCl_3$)} was synthesized in 8% overall yield in 10 steps (longest-linear sequence) from 11-bromoundecan-1-ol. These optimized conditions were also applied to the synthesis of nakinadine A **28** from **23** using aldehyde **4**[3,13] (in place of **5**) in the reductive *N*-alkylation step, as we have previously described,[5] thus facilitating its synthesis in 10% overall yield in 10 steps (longest-linear sequence) from 11-bromoundecan-1-ol (Scheme 7).

The synthesis of **31**, the C(2)-epimer of **27**, was now undertaken. Deprotection of the *N*-*tert*-butylsulfinyl group from **24** (94:3:3 dr) using HCl (1.25 M in MeOH)[9] gave **29**, which was reacted with aldehyde **5** [97:3 dr, (*E*):(*Z*) ratio][4,5,13] in the presence of $NaB(OAc)_3H$ to give **30** in 58% yield and ~93% diastereoisomeric purity.[18] Hydrolysis of **30** using HCl (3.0 M aq) at 70 °C, followed by purification, gave **31** in 58% yield, ~93% diastereoisomeric purity,[18] and >98% ee [based upon the enantiomeric purity of (*R*)-**1**]. Therefore, **31** {$[\alpha]_D^{20}$ +8.1 (*c* 1.0 in $CHCl_3$)} was synthesized in 8% overall yield in 11 steps (longest-linear sequence) from 11-bromoundecan-1-ol. As previously described,[5] **32** was prepared from **24**, via an analogous route using aldehyde **4**[3,13] (in place of **5**) in the

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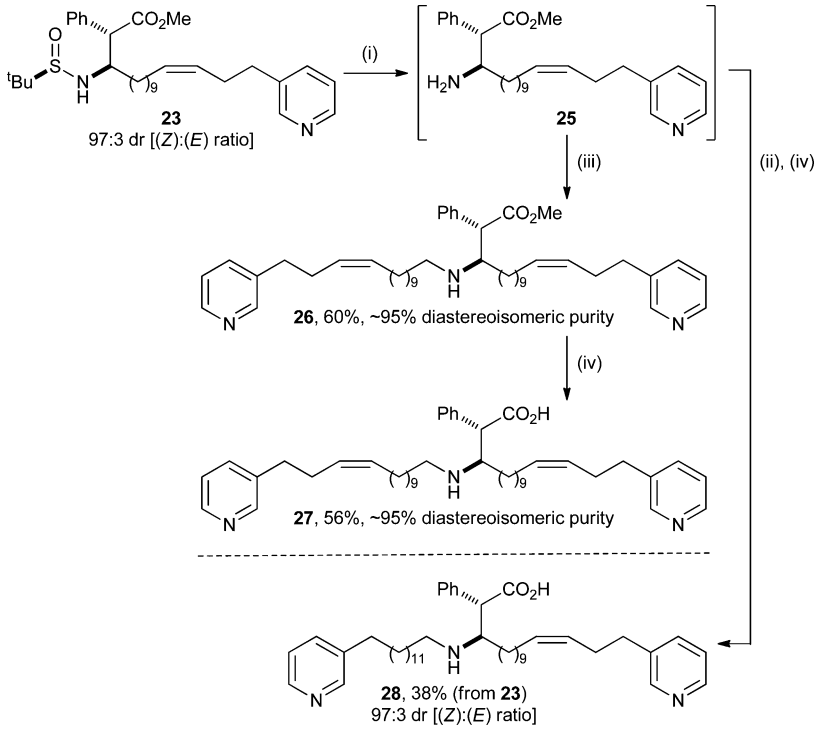
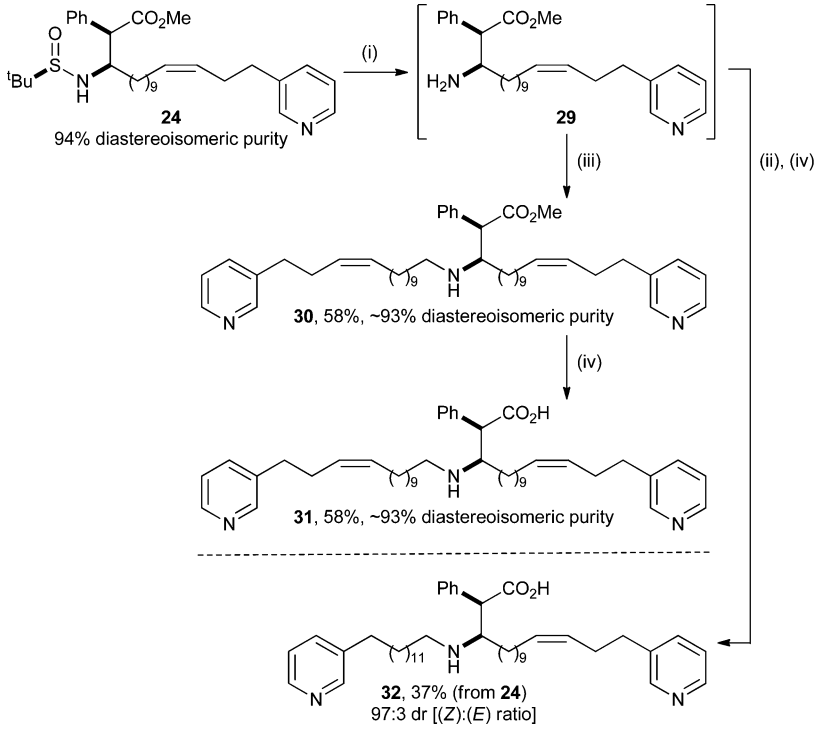
Scheme 7[a]



[a]Reagents and conditions: (i) HCl (1.25 M in MeOH), rt, 2 h, then satd aq $NaHCO_3$; (ii) **4**, $NaB(OAc)_3H$, AcOH, 1,2-dichloroethane, rt, 16 h; (iii) **5**, $NaB(OAc)_3H$, AcOH, 1,2-dichloroethane, rt, 16 h; (iv) HCl (3.0 M aq), 70 °C, 80 h.

Scheme 8[a]



[a]Reagents and conditions: (i) HCl (1.25 M in MeOH), rt, 2 h, then satd aq $NaHCO_3$; (ii) **4**, $NaB(OAc)_3H$, AcOH, 1,2-dichloroethane, rt, 16 h; (iii) **5**, $NaB(OAc)_3H$, AcOH, 1,2-dichloroethane, rt, 16 h; (iv) HCl (3.0 M aq), 70 °C, 80 h.

reductive *N*-alkylation, in 9% overall yield in 11 steps (longest-linear sequence) from 11-bromoundecan-1-ol (Scheme 8).

Comparison of the ^1H and ^{13}C NMR spectroscopic data reported for natural nakinadine D by Kobayashi et al.[2] with those of the synthetic materials **17** and **21** (recorded in

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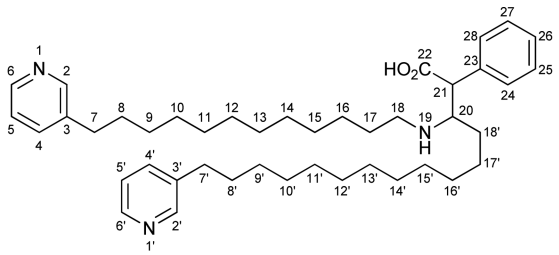
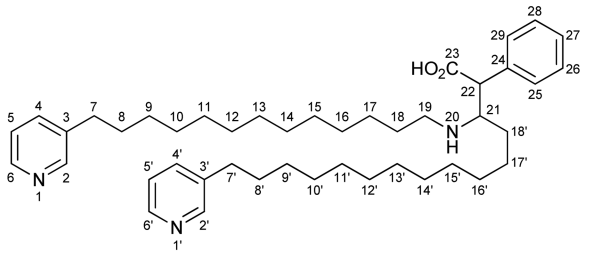
neutralized $CDCl_3$ at a concentration of 127 mM) showed that the NMR spectra were generally very similar (Figure 3). However, focusing on the peaks corresponding to the protons and carbons in the key region of the α-phenyl-β-amino acid moiety [i.e., C(20)*H*, C(21)*H*, *C*(20), *C*(21), and *C*(23)], the chemical shifts in both the ^1H and the ^{13}C NMR spectra of **17** matched more closely with those of the natural product than those of the corresponding C(2)-epimer **21**. This supports the relative (*RS,SR*)-configuration originally proposed by Kobayashi et al. for this natural product.[2] Similar observations were made regarding the chemical shifts of the respective protons and carbons in the NMR spectra for natural nakinadine E[2] when compared to those of the synthetic material **18** and the C(2)-epimer **22** (Figure 4), and natural nakinadine F[2] when compared to those of the synthetic material **27** and the C(2)-epimer **31** (Figure 5). As Kobayashi et al. reported a specific rotation value for nakinadine A only,[1] it is impossible to assign



	proton #	nakinadine D δ_H (ppm)	(*2S,3R*)-**17** δ_H (ppm)	(*2R,3R*)-**21** δ_H (ppm)
pyridin-3-yl moieties	2, 6, 2', 6'	8.44 (4H, m)	8.44 (4H, m)	8.45 (4H, m)
	4, 4'	7.49 (2H, m)	7.48 (2H, m)	7.49 (2H, m)
	5, 5'	7.20 (2H, m)	7.23 (in 5H, m)	7.21 (in 3H, m)
alkyl chains	7, 7'	2.60 (4H, m)*	2.60 (4H, m)	2.61 (in 5H, m)
	8–17, 8'–18'	1.1–1.7 (42H, m)	1.1–1.7 (42H, m)	1.0–1.8 (42H, m)
	18-A	2.72 (1H, m)	2.71 (1H, m)	2.61 (in 5H, m)
	18-B	2.82 (1H, m)	2.83 (1H, m)	2.88 (1H, m)
β-amino acid moiety	20	2.98 (1H, br s)	3.14 (1H, m)	3.35 (1H, m)
	21	3.84 (1H, br s)	3.82 (1H, br d)	3.71 (1H, m)
phenyl ring	24, 28	7.32 (in 4H, m)	7.34 (2H, d)	7.31 (in 4H, m)
	25, 27	7.32 (in 4H, m)	7.23 (in 5H, m)	7.31 (in 4H, m)
	26	7.19 (1H, m)	7.23 (in 5H, m)	7.21 (in 3H, m)

	carbon #	nakinadine D δ_C (ppm)	(*2S,3R*)-**17** δ_C (ppm)	(*2R,3R*)-**21** δ_C (ppm)
pyridin-3-yl moieties	2, 2'	149.6	149.8	149.9
	3, 3'	136.9	138.0	137.9
	4, 4'	135.5	135.8	135.7
	5, 5'	122.9	123.3	123.2
	6, 6'	146.8	147.0	147.1
alkyl chains	7, 7'	32.7	33.0	33.0
	8–17, 8'–18'	26.6, 26.9, 28–30, 30.8	26.3, 26.9, 28–30, 31.1	24.9, 26.8, 29–30, 31.1
	18	44.9	45.7	44.6
β-amino acid moiety	20	59.5	59.9	60.8
	21	51.9	51.7	54.3
	22	176.0	175.1	176.7
phenyl ring	23	135.8	135.3	139.1
	24, 28	129.4	129.6	128.7
	25, 27	128.2	128.7	128.5
	26	127.0	127.5	127.0

Figure 3. ^1H and ^{13}C NMR spectroscopic data for natural nakinadine D (unknown concentration in $CDCl_3$), synthetic material **17** (127 mM in neutralized $CDCl_3$), and the C(2)-epimer **21** (127 mM in neutralized $CDCl_3$). The numbering convention adopted by Kobayashi et al. (ref 2) has also been adopted here. *In the ^1H NMR spectroscopic data reported for the natural product, the resonance corresponding to C(7)H_2 and C(7′)H_2 is defined as a triplet with coupling constant values of 7.8 and 7.5 Hz [*sic*]; it is, therefore, quoted here as a multiplet.



	proton #	nakinadine E δ_H (ppm)	(*2S,3R*)-**18** δ_H (ppm)	(*2R,3R*)-**22** δ_H (ppm)
pyridin-3-yl moieties	2, 6, 2', 6'	8.41 (4H, m)	8.43 (4H, m)	8.47 (4H, m)
	4, 4'	7.50 (2H, m)	7.49 (2H, m)	7.49 (2H, m)
	5, 5'	7.21 (2H, m)	7.22 (in 5H, m)	7.18 (in 3H, m)
alkyl chains	7, 7'	2.61 (4H, m)	2.60 (4H, m)	2.59 (in 5H, m)
	8–18, 8'–18'	1.0–1.8 (44H, m)	1.1–1.7 (44H, m)	1.0–1.8 (44H, m)
	19-A	2.72 (1H, m)	2.70 (1H, m)	2.59 (in 5H, m)
	19-B	2.85 (1H, m)	2.84 (1H, m)	2.87 (1H, m)
β-amino acid moiety	21	3.05 (1H, br s)	3.14 (1H, m)	3.34 (1H, m)
	22	3.87 (1H, br s)	3.84 (1H, br d)	3.70 (1H, m)
phenyl ring	25, 29	7.33 (in 4H, m)	7.35 (2H, d)	7.30 (in 4H, m)
	26, 28	7.33 (in 4H, m)	7.22 (in 5H, m)	7.30 (in 4H, m)
	27	7.20 (1H, m)	7.22 (in 5H, m)	7.18 (in 3H, m)

	carbon #	nakinadine E δ_C (ppm)	(*2S,3R*)-**18** δ_C (ppm)	(*2R,3R*)-**22** δ_C (ppm)
pyridin-3-yl moieties	2, 2'	149.6	149.9	149.9
	3, 3'	136.9	138.0	138.0
	4, 4'	135.5	135.8	135.7
	5, 5'	122.9	123.2	123.3
	6, 6'	146.8	147.1	147.1
alkyl chains	7, 7'	32.7	33.0	33.0
	8–18, 8'–18'	26.6, 26.9, 28–30, 30.8	26.3, 26.9, 28–30, 31.1	25.0, 26.7, 26.8, 29–30, 31.1
	19	44.9	45.5	44.6
β-amino acid moiety	21	59.5	59.9	60.8
	22	51.9	51.9	54.2
	23	176.0	175.6	176.7
phenyl ring	24	135.8	135.6	139.0
	25, 29	129.4	129.6	128.7
	26, 28	128.2	128.6	128.5
	27	127.0	127.4	127.0

Figure 4. ^1H and ^{13}C NMR spectroscopic data for natural nakinadine E (unknown concentration in $CDCl_3$), synthetic material **18** (127 mM in neutralized $CDCl_3$), and the C(2)-epimer **22** (127 mM in neutralized $CDCl_3$). The numbering convention adopted by Kobayashi et al. (ref 2) has also been adopted here.

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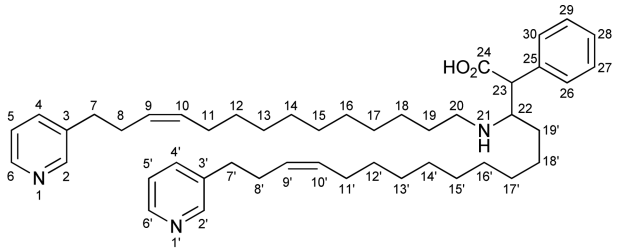

	proton #	nakinadine F δ_H (ppm)	(2*S*,3*R*,*Z*)-**27** δ_H (ppm)	(2*R*,3*R*,*Z*)-**31** δ_H (ppm)
pyridin-3-yl moieties	2, 6, 2', 6'	8.40 (4H, m)	8.43 (4H, m)	8.44 (4H, m)
	4, 4'	7.49 (2H, m)	7.50 (2H, m)	7.51 (2H, m)
	5, 5'	7.20 (2H, m)	7.24 (in 5H, m)	7.21 (in 3H, m)
alkyl chains	7, 7'	2.60 (2H, m), 2.65 (2H, m)	2.69 (in 5H, m)	2.64 (in 5H, m)
	8, 8'	2.35 (4H, m)	2.35 (4H, m)	2.36 (4H, m)
	9, 9', 10, 10'	5.38 (4H, m)	5.39 (4H, m)	5.39 (4H, m)
	11, 11'	1.0–1.7 (in 36H, m)	1.93 (4H, m)	1.92 (4H, m)
	12–19, 12'–19'	1.0–1.7 (in 36H, m)	1.1–1.7 (32H, m)	1.0–1.8 (32H, m)
	20-A	2.70 (1H, m)	2.69 (in 5H, m)	2.64 (in 5H m)
	20-B	2.80 (1H, m)	2.82 (1H, m)	2.91 (1H, m)
β-amino acid moiety	22	3.01 (1H, br s)	3.11 (1H, m)	3.36 (1H, m)
	23	3.84 (1H, br s)	3.84 (1H, m)	3.72 (1H, d)
phenyl ring	26, 30	7.31 (in 4H, m)	7.34 (2H, m)	7.31 (in 4H, m)
	27, 29	7.31 (in 4H, m)	7.24 (in 5H, m)	7.31 (in 4H, m)
	28	7.18 (1H, m)	7.24 (in 5H, m)	7.21 (in 3H, m)

	carbon #	nakinadine F δ_C (ppm)	(2*S*,3*R*,*Z*)-**27** δ_C (ppm)	(2*R*,3*R*,*Z*)-**31** δ_C (ppm)
pyridin-3-yl moieties	2, 2'	149.6	149.8, 149.9	150.0
	3, 3'	136.9	137.3	137.2
	4, 4'	135.5	135.97, 136.04	135.9
	5, 5'	122.9	123.2	123.2
	6, 6'	146.8	147.1, 147.2	147.3
alkyl chains	7, 7'	32.7	33.0	33.0
	8, 11–19, 8', 11'–19'	26.6, 26.9, 28–30*	26.3, 26.9, 27–30	24.7, 26.8, 27–30
	9, 9'	127.4	127.7	127.7
	10, 10'	131.1	131.4	131.4
	20	44.9	45.8	44.8
β-amino acid moiety	22	59.5	60.0	60.7
	23	51.9	51.9	54.4
	24	176.0	175.3	176.7
phenyl ring	25	135.8	135.5	138.9
	26, 30	129.4	129.6	128.8
	27, 29	128.2	128.6	128.5
	28	127.0	127.4	127.1

Figure 5. ^{1}H and ^{13}C NMR spectroscopic data for natural nakinadine F (unknown concentration in $CDCl_3$), synthetic material **27** (127 mM in neutralized $CDCl_3$), and the C(2)-epimer **31** (127 mM in neutralized $CDCl_3$). The numbering convention adopted by Kobayashi et al. (ref 2) has also been adopted here. *The ^{13}C NMR spectroscopic data for the natural product includes the following resonances (in ppm): 28–30 (14C) and 28.4 [*sic*] (2C); therefore, only a 28–30 ppm range is reported here.

for certain the absolute configurations of nakinadines D–F by comparison with our synthetic samples in the absence of authentic samples of the natural products.[19] Nonetheless, we have previously assigned the absolute (2*S*,3*R*,*Z*)-configuration to natural nakinadine A by comparison of the ^{1}H and ^{13}C NMR spectroscopic data and specific rotation value reported for the natural material[1] and those of our synthetic sample **28** and the C(2)-epimer **32**.[5] The established absolute (2*S*)-configurations of nakinadines A–C led us to speculate that the members of this alkaloid family are homochiral at C(2) [i.e., nakinadines D–F also share the absolute (2*S*)-configuration].[5] On the basis of this hypothesis, the data contained herein support assignment of the (2*S*,3*R*)-configuration to natural nakinadines D–F.

CONCLUSION

In conclusion, both the *syn*- and *anti*-diastereoisomers of the reported structures of nakinadines D–F (as well as those of nakinadine A) have been synthesized via a common route from commercially available dodecane-1,12-diol or 11-bromoundecan-1-ol, in 8–16% overall yield in 11 steps or fewer in all cases. Comparison of the spectroscopic data of the natural material with these synthetic samples confirms the relative (*RS*,*SR*)-configuration originally assigned to these alkaloids. Unfortunately, the absolute configurations of nakinadines D–F cannot be unambiguously assigned owing to the unavailability of specific rotation (or other diagnostic) data. Nonetheless, on the basis of the absolute (2*S*,3*R*,*Z*)-configuration established for nakinadine A, the absolute (2*S*)-configurations established for nakinadines B and C, and on the assumption that the members of this alkaloid family are homochiral at C(2), the data contained herein support assignment of the absolute (2*S*,3*R*)-configurations to nakinadines D–F.

EXPERIMENTAL SECTION

General Experimental Details. Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[20] Organic layers were dried over Na_2SO_4. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. Deuterated chloroform was neutralized (to record the NMR spectra of the nakinadine alkaloids and their diastereoisomers) by passage through a column of activated basic alumina (Brockmann I). The field was locked by external referencing to the relevant deuteron resonance. ^{1}H–^{1}H COSY and ^{1}H–^{13}C HMQC analyses were used to establish atom connectivity. Accurate mass measurements were run on a MicroTOF instrument internally calibrated with polyalanine.

X-ray Crystal Structure Determination.[15] Data were collected using graphite monochromated Cu–Kα radiation via standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[21]

12-(Pyridin-3′-yl)dodecanal 3. *Step 1*: BuLi (2.40 M in hexanes, 8.32 mL, 20.0 mmol) was added dropwise via syringe to a stirred solution of diisopropylamine (2.80 mL, 20.0 mmol) in THF (60 mL) at 0 °C. After 1 h, the solution was cooled to −78 °C and a solution of 3-picoline (1.94 mL, 20.0 mmol) in THF (10 mL) was added. After a further 30 min, a solution of 11-bromoundecan-1-ol (2.00 g, 7.99

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mmol) in THF (10 mL) was added. After 10 min, the cooling bath was taken away and the reaction mixture was allowed to warm to rt over 16 h, before the sequential addition of satd aq NH_4Cl (20 mL) and H_2O (30 mL). The phases were separated, the aqueous phase was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution 20% → 70% EtOAc in 30−40 °C petrol) gave 12-(pyridin-3′-yl)dodecan-1-ol as an off-white solid (1.69 g, 80%);[12] mp 46−47 °C; {lit.[12] 48−50 °C}; δ_H (400 MHz, $CDCl_3$) 1.22−1.41 (16H, m, C(3)H_2−C(10)H_2), 1.52−1.67 (4H, m, C(2)H_2, C(11)H_2), 2.61 (2H, t, *J* 7.7, C(12)H_2), 3.64 (2H, t, *J* 6.7, C(1)H_2), 7.21 (1H, dd, *J* 7.8, 4.8, C(5′)*H*), 7.47−7.54 (1H, m, C(4′)*H*), 8.40−8.48 (2H, m, C(2′)*H*, C(6′)*H*).

Step 2: IBX (303 mg, 1.08 mmol) was added to a stirred solution of 12-(pyridin-3′-yl)dodecan-1-ol (100 mg, 0.36 mmol) in EtOAc (2 mL) at rt, and the resultant mixture was stirred at 80 °C for 3 h, before being allowed to cool to rt and filtered though Celite (eluent EtOAc, ∼10 mL). The filtrate was concentrated *in vacuo* to give **3**[13] as a yellow oil (93 mg, 98%); δ_H (400 MHz, $CDCl_3$) 1.11−1.35 (14H, m, C(4)H_2−C(10)H_2), 1.48−1.64 (4H, m, C(3)H_2, C(11)H_2), 2.36 (2H, td, *J* 7.4, 1.9, C(2)H_2), 2.54 (2H, t, *J* 7.7, C(12)H_2), 7.16 (1H, dd, *J* 7.7, 4.9, C(5′)*H*), 7.43−7.48 (1H, m, C(4′)*H*), 8.35−8.42 (2H, m, C(2′)*H*, C(6′)*H*), 9.70 (1H, t, *J* 1.9, C(1)*H*).

(*R*$_S$,*E*)-*N*-[13-(Pyridin-3′-yl)tridec-1-ylidene]-*tert*-butylsulfinamide 6. (*R*)-**1** (866 mg, 7.15 mmol, >98% ee), PPTS (90 mg, 0.36 mmol), and $MgSO_4$ (4.30 g, 35.7 mmol) were sequentially added to a stirred solution of **4**[3,13] (1.97 g, 7.15 mmol) in CH_2Cl_2 (10 mL), and the resultant suspension was stirred at rt for 16 h, before being filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent, 30−40 °C petrol/EtOAc, 60:40) gave **6** as a pale yellow oil (2.43 g, 90%, >99:1 dr [(*E*):(*Z*)] ratio); $[\alpha]_D^{20}$ −158.0 (*c* 1.0 in $CHCl_3$); ν_{max} 1084, 1622; δ_H (400 MHz, $CDCl_3$) 1.17 (9H, s, CMe_3), 1.20−1.37 (16H, m, C(4)H_2−C(11)H_2), 1.54−1.64 (4H, m, C(3)H_2, C(12)H_2), 2.48 (2H, td, *J* 7.3, 4.8, C(2)H_2), 2.57 (2H, t, *J* 7.7, C(13)H_2), 7.17 (1H, dd, C(5′)*H*), 7.43−7.49 (1H, m, C(4′)*H*), 8.04 (1H, t, *J* 4.8, C(1)*H*), 8.37−8.45 (2H, m, C(2′)*H*), C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 22.3 (CMe_3), 25.5 (*C*(3)), 29.1, 29.2, 29.3, 29.36, 29.41, 29.48, 29.51, 29.53 (*C*(4)−*C*(11)), 31.1 (*C*(12)), 33.0 (*C*(13)), 36.1 (*C*(2)), 56.5 (CMe_3), 123.2 (*C*(5′)), 135.8 (*C*(4′)), 137.9 (*C*(3′)), 147.1 (*C*(6′)), 149.9 (*C*(2′)), 169.8 (*C*(1)); *m*/*z* (ESI$^+$) 379 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{39}N_2OS^+$ ([M + H]$^+$) requires 379.2778; found 379.2769.

Methyl (2*S*,3*R*,*R*$_S$)-2-Phenyl-3-(*N*-*tert*-butylsulfinamido)-15-(pyridin-3′-yl)pentadecanoate 9. MeMgBr (2.86 M in Et_2O, 0.56 mL, 1.59 mmol) was added dropwise to a stirred suspension of **2** (0.24 mL, 1.72 mmol) and $MgBr_2$ (1.21 g, 6.61 mmol) in THF (10 mL) at −78 °C. After 1 h, a solution of **6** (500 mg, 1.32 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (5 mL) was added via syringe, and the resultant mixture was stirred at −78 °C for 6 h, before the addition of satd aq NH_4Cl (5 mL). After warming to rt over 15 min, the reaction mixture was diluted with EtOAc (20 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (20 mL), and the combined organic extracts were washed with brine (10 mL), then dried, and concentrated in vacuo to give an 86:14 mixture of **9** and **10**, respectively. Purification via recrystallization (Et_2O/petrol) gave **9** as a white solid (425 mg, 61%, >99:1 dr); mp 65−67 °C; $[\alpha]_D^{20}$ −51.2 (*c* 1.0 in $CHCl_3$); ν_{max} 1068, 1456, 1734 (C═O); δ_H (500 MHz, C_6D_6) 0.99 (9H, s, CMe_3), 1.12−1.42 (19H, m, C(6)H_2−C(14)H_2, C(5)H_A), 1.50−1.70 (2H, m, C(4)H_A, C(5)H_B), 1.82−1.93 (1H, m, C(4)H_B), 2.27 (2H, t, *J* 7.7, C(15)H_2), 3.30 (3H, s, O*Me*), 3.93 (1H, d, *J* 6.9, N*H*), 3.97−4.04 (1H, m, C(3)*H*), 4.27 (1H, d, *J* 6.0, C(2)*H*), 6.76 (1H, dd, *J* 7.9, 4.7, C(5′)*H*), 6.99−7.05 (2H, m, C(4′)*H*, *p*-*Ph*), 7.07−7.13 (2H, m, *m*-*Ph*), 7.29−7.33 (2H, m, *o*-*Ph*), 8.47−8.53 (1H, m, C(6′)*H*), 8.54−8.62 (1H, m, C(2′)*H*); δ_C (125 MHz, C_6D_6) 22.9 (CMe_3), 26.6 (*C*(5)), 29.8, 30.1, 30.2, 30.3, 30.4 (*C*(6)−*C*(13)), 31.8 (*C*(14)), 32.8 (*C*(4)), 33.5 (*C*(15)), 52.0 (O*Me*), 55.8 (CMe_3), 57.2 (*C*(2)), 58.7 (*C*(3)), 123.6 (*C*(5′)), 128.7 (*p*-*Ph*), 129.2 (*m*-*Ph*), 130.4 (*o*-*Ph*), 135.5 (*C*(4′)), 136.6 (*i*-*Ph*), 138.1 (*C*(3′)), 148.2 (*C*(6′)), 151.0 (*C*(2′)), 173.2 (*C*(1)); *m*/*z* (ESI$^+$) 529 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{49}N_2O_3S^+$ ([M + H]$^+$) requires 529.3458; found 529.3454. The mother liquor was concentrated in vacuo. Purification via flash column chromatography gave **10** as a colorless oil (63 mg, 9%, 98:2 dr); $[\alpha]_D^{20}$ +14.8 (*c* 1.0 in $CHCl_3$); ν_{max} 1069, 1456, 1736 (C═O); δ_H (400 MHz, C_6D_6) 1.03 (9H, s, CMe_3), 1.10−1.43 (20H, m, C(5)H_2−C(14)H_2), 1.44−1.58 (1H, m, C(4)H_A), 1.60−1.74 (1H, m, C(4)H_B), 2.26 (2H, t, *J* 7.6, C(15)H_2), 3.33 (3H, s, O*Me*), 3.48 (1H, d, *J* 8.6, N*H*), 4.04−4.14 (1H, m, C(3)*H*), 4.26 (1H, d, *J* 7.8, C(2)*H*), 6.75 (1H, dd, *J* 7.7, 4.7, C(5′)*H*), 6.99−7.07 (2H, m, C(4′)*H*, *p*-*Ph*), 7.10−7.16 (2H, m, *m*-*Ph*), 7.44−7.52 (2H, m, *o*-*Ph*), 8.48−8.53 (1H, m, C(6′)*H*), 8.55−8.59 (1H, m, C(2′)*H*); δ_C (100 MHz, C_6D_6) 23.0 (CMe_3), 26.3 (*C*(5)), 29.8, 29.9, 30.1, 30.27, 30.33, 30.4 (*C*(6)−*C*(13)), 31.7 (*C*(14)), 33.3 (*C*(4)), 33.5 (*C*(15)), 52.1 (O*Me*), 56.1 (CMe_3), 58.0 (*C*(2)), 59.3 (*C*(3)), 123.6 (*C*(5′)), 128.2 (*p*-*Ph*), 129.2 (*m*-*Ph*), 130.4 (*o*-*Ph*), 135.6 (*C*(4′)), 136.4 (*i*-*Ph*), 138.1 (*C*(3′)), 148.2 (*C*(6′)), 151.0 (*C*(2′)), 173.1 (*C*(1)); *m*/*z* (ESI$^+$) 529 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{49}N_2O_3S^+$ ([M + H]$^+$) requires 529.3458; found 529.3454.

Enolate Trapping Experiment. LiHMDS (1.0 M in THF, 0.36 mL, 0.36 mmol) was added dropwise to a stirred suspension of **2** (47 μL, 0.33 mmol) and LiCl (72 mg, 1.66 mmol) in THF (1 mL) at −78 °C. After 30 min, TMSCl (63 μL, 0.50 mmol) was added dropwise, and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give a 90:10 mixture of the (*E*)- and (*Z*)-enolates, respectively.[22] Data for (*E*)-enolate: δ_H (400 MHz, $CDCl_3$) 0.37 (9H, s, OSiMe_3), 3.74 (3H, s, O*Me*), 4.72 (1H, s, C*H*), 7.03−7.10 (1H, m, *Ph*), 7.25−7.30 (2H, m, *Ph*), 7.43−7.47 (2H, m, *Ph*). Data for (*Z*)-enolate: δ_H (400 MHz, $CDCl_3$) 0.33 (9H, s, SiMe_3), 3.70 (3H, s, O*Me*), 4.63 (1H, s, C*H*), 7.02−7.09 (1H, m, *Ph*), 7.17−7.40 (2H, m, *Ph*), 7.45−7.50 (2H, m, *Ph*).

Methyl (2*R*,3*R*,*R*$_S$)-2-Phenyl-3-(*N*-*tert*-butylsulfinamido)-15-(pyridin-3′-yl)pentadecanoate 10. *Method A (from 9).* Na (13 mg, 0.57 mmol) was added to a solution of **9** (60 mg, 0.11 mmol, >99:1 dr) in MeOH (0.5 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 8 h, before the addition of satd aq NH_4Cl (1 mL). The reaction mixture was diluted with EtOAc (10 mL), and the phases were separated. The aqueous layer was extracted with EtOAc (5 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give a 20:80 mixture of **9** and **10**, respectively. Purification via flash column chromatography gave **9** as a white solid (6 mg, 10%, >99:1 dr); $[\alpha]_D^{20}$ −49.5 (*c* 1.0 in $CHCl_3$). Further elution gave **10** as a colorless oil (39 mg, 65%, 98:2 dr); $[\alpha]_D^{20}$ +14.2 (*c* 1.0 in $CHCl_3$).

Method B (from 6). Step 1. MeMgBr (2.86 M in Et_2O, 0.39 mL, 1.11 mmol) was added dropwise via syringe to a stirred suspension of **2** (0.17 mL, 1.20 mmol) and $MgBr_2$ (850 mg, 4.62 mmol) in THF (5 mL) at −78 °C. After 1 h, a solution of **6** (348 mg, 0.92 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (5 mL) at −78 °C was added, and the resultant suspension was stirred at −78 °C for 6 h, before the addition of satd aq NH_4Cl (5 mL). The resultant mixture was allowed to warm to rt over 15 min and then diluted with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (20 mL), and the combined organic extracts were washed with brine (10 mL), then dried, and concentrated *in vacuo* to give an 86:14 mixture of **9** and **10**, respectively, as a yellow oil (490 mg).

Step 2. Na (106 mg, 4.62 mmol) was added to a stirred solution of the residue from the previous step (490 mg) in MeOH (5 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 8 h before the dropwise addition of satd aq NH_4Cl (5 mL). The resultant mixture was allowed to warm to rt over 15 min and then diluted with CH_2Cl_2 (20 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give a 20:80 mixture of **9** and **10**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 40:60) gave **9** as a white solid (44 mg, 9% from **6**, >99:1 dr); $[\alpha]_D^{20}$ −51.0 (*c* 1.0 in $CHCl_3$). Further elution gave **10** as a colorless oil (291 mg, 60% from **6**, 98:2 dr); $[\alpha]_D^{20}$ +15.0 (*c* 1.0 in $CHCl_3$).

Methyl (2*S*,3*R*,*S*$_S$)-2-Phenyl-3-(*N*-*tert*-butylsulfinamido)-15-(pyridin-3′-yl)pentadecanoate *ent*-11. *Step 1.* A solution of **9** (69 mg, 0.13 mmol, >99:1 dr) in HCl (1.25 M in MeOH, 2 mL) was stirred at rt for 2 h and then concentrated *in vacuo*. The residue was

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partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (5 mL), and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), then dried, and concentrated *in vacuo* to give **13** as a white solid (55 mg).

Step 2. Et_3N (20 μL, 0.14 mmol) and (*RS*)-*tert*-butylsulfinyl chloride (16 μL, 0.13 mmol) were sequentially added to a stirred solution of the residue **13** from the previous step (55 mg) in CH_2Cl_2 (2 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 2 h, before being concentrated *in vacuo*. The residue was partitioned between satd aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL), the phases were separated, and the organic layer was washed with satd aq $NaHCO_3$ (5 mL), then dried, and concentrated *in vacuo* to give an ∼50:50 mixture of **9** and *ent*-**11**. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 40:60) gave a 36:64 mixture of **9** and *ent*-**11**, respectively, as a white solid (41 mg, 60%). Data for *ent*-**11**: δ_H (500 MHz, C_6D_6) [selected peaks] 0.84 (9H, s, CMe_3), 2.27 (2H, t, *J* 7.6, C(15)H_2), 3.08 (1H, d, *J* 7.1, N*H*), 3.25 (3H, s, O*Me*), 3.85 (1H, d, *J* 9.1, C(2)*H*), 4.02−4.12 (1H, m, C(3)*H*), 6.76 (1H, dd, *J* 7.7, 4.7, C(5′)*H*), 6.99−7.06 (2H, m, C(4′)*H*, *p*-*Ph*), 7.08−7.15 (2H, m, *m*-*Ph*), 7.41−7.48 (2H, m, *o*-*Ph*), 8.45−8.52 (1H, m, C(6′)*H*), 8.54−8.60 (1H, m, C(2′)*H*); δ_C (125 MHz, C_6D_6) [selected peaks] 22.8 (CMe_3), 26.5 (*C*(5)), 31.8 (*C*(14)), 33.5 (*C*(15)), 34.8 (*C*(4)), 51.8 (O*Me*), 55.8 (CMe_3), 58.6 (*C*(2)), 60.4 (*C*(3)), 123.6 (*C*(5′)), 128.3 (*p*-*Ph*), 129.1 (*m*-*Ph*), 130.4 (*o*-*Ph*), 135.6 (*C*(4′)), 137.3 (*i*-*Ph*), 138.2 (*C*(3′)), 148.1 (*C*(6′)), 151.0 (*C*(2′)), 173.1 (*C*(1)).

Methyl (2*R*,3*R*,S_S)-2-Phenyl-3-(*N*-*tert*-butylsulfinamido)-15-(pyridin-3′-yl)pentadecanoate *ent*-12. *Step 1.* A solution of **10** (64 mg, 0.12 mmol, 98:2 dr) in HCl (1.25 M in MeOH, 2 mL) was stirred at rt for 2 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (10 mL), and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 10 mL), then dried, and concentrated *in vacuo* to give **14** as a white solid (51 mg).

Step 2. Et_3N (18 μL, 0.13 mmol) and (*RS*)-*tert*-butylsulfinyl chloride (15 μL, 0.12 mmol) were sequentially added to a stirred solution of the residue **14** from the previous step (51 mg) in CH_2Cl_2 (2 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 2 h, before being concentrated *in vacuo*. The residue was partitioned between satd aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL), the phases were separated, and the organic layer was washed with satd aq $NaHCO_3$ (5 mL), then dried, and concentrated *in vacuo* to give an ∼50:50 mixture of **10** and *ent*-**12**. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 40:60) gave a 32:68 mixture of **10** and *ent*-**12**, respectively, as a white solid (32 mg, 50%). Data for *ent*-**12**: δ_H (500 MHz, C_6D_6) [selected peaks] 1.07 (9H, s, CMe_3), 2.26 (2H, t, *J* 7.6, C(15)H_2), 3.30 (3H, s, O*Me*), 3.89−4.00 (3H, m, N*H*, C(2)*H*, C(3)*H*), 6.76 (1H, dd, *J* 7.7, 4.7, C(5′)*H*), 7.26 (2H, d, *J* 7.3, *o*-*Ph*), 8.50 (1H, d, *J* 4.4, C(6′)*H*), 8.55−8.60 (1H, m, C(2′)*H*); δ_C (125 MHz, C_6D_6) [selected peaks] 23.0 (CMe_3), 25.9 (*C*(5)), 52.0 (O*Me*), 55.9 (CMe_3), 59.0 (*C*(2)), 60.3 (*C*(3)), 135.6 (*C*(4′)), 137.9 (*i*-*Ph*), 138.1 (*C*(3′)), 148.2 (*C*(6′)), 151.0 (*C*(2′)), 173.8 (*C*(1)).

Methyl (2*S*,3*R*)-2-Phenyl-3-{*N*-[12″-(pyridin-3‴-yl)dodecyl]-amino}-15-(pyridin-3′-yl)pentadecanoate 15. *Step 1.* A solution of **9** (40 mg, 0.076 mmol, >99:1 dr) in HCl (1.25 M in MeOH, 1.5 mL) was stirred at rt for 2 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (5 mL), and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), then dried, and concentrated *in vacuo* to give **13** as a white solid (31 mg).

Step 2. A solution of 3^{13} (21 mg, 0.079 mmol) in 1,2-dichloroethane (1 mL) was added to a stirred solution of the residue **13** from the previous step (31 mg) in 1,2-dichloroethane (1 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (32 mg, 0.152 mmol) were added, and the resultant mixture was stirred at rt for 16 h, before satd aq $NaHCO_3$ (5 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **15** as a pale yellow oil (32 mg, 63% from **9**, >99:1 dr); $[\alpha]_D^{20}$ −16.6 (*c* 1.0 in $CHCl_3$); ν_{max} 1735 (C═O); δ_H (500 MHz, C_6D_6) 1.11−1.47 (38H, m, part of C(4)H_2−C(14)H_2, C(2″)H_2−C(11″)H_2), 1.57−1.76 (4H, part of C(4)H_2−C(14)H_2, C(2″)H_2−C(11″)H_2), 2.24−2.30 (4H, m, C(15)H_2, C(12″)H_2), 2.37−2.45 (1H, m, C(1″)H_A), 2.48−2.56 (1H, m, C(1″)H_B), 3.30 (3H, s, O*Me*), 3.45−3.51 (1H, m, C(3)*H*), 3.85 (1H, d, *J* 9.5, C(2)*H*), 6.74−6.78 (2H, m, C(5′)*H*, C(5‴)*H*), 6.98−7.09 (3H, m, C(4′)*H*, C(4‴)*H*, *p*-*Ph*), 7.12−7.17 (2H, m, *m*-*Ph*), 7.48−7.53 (2H, m, *o*-*Ph*), 8.49−8.52 (2H, m, C(6′)*H*, C(6‴)*H*), 8.54−8.61 (2H, m, C(2′)*H*, C(2‴)*H*); δ_C (125 MHz, C_6D_6) 26.2, 27.9, 29.8, 30.2, 30.3, 30.4, 30.5, 30.7, 31.2, 31.8, 33.0 (*C*(4)−*C*(14), *C*(2″)−*C*(11″)), 33.5 (*C*(15), *C*(12″), 46.8 (*C*(1″)), 51.7 (O*Me*), 57.1 (*C*(2)), 60.9 (*C*(3)), 123.5 (*C*(5′), *C*(5‴)), 128.0 (*p*-*Ph*), 129.2, 129.8 (*o*,*m*-*Ph*), 135.5 (*C*(4′), *C*(4‴)), 138.07, 138.09, 138.14 (*C*(3′), *C*(3‴), *i*-*Ph*), 148.2 (*C*(6′), *C*(6‴)), 151.0 (*C*(2′), *C*(2‴)), 173.8 (*C*(1)); *m*/*z* (ESI$^+$) 671 ([M + H]$^+$, 5%), 336 ([M + 2H]$^{2+}$, 100%), 224 ([M + 3H]$^{3+}$, 90%); HRMS (ESI$^+$) $C_{44}H_{68}N_3O_2^+$ ([M + H]$^+$) requires 670.5306; found 670.5302.

Methyl (2*S*,3*R*)-2-Phenyl-3-{*N*-[13″-(pyridin-3‴-yl)tridecyl]-amino}-15-(pyridin-3′-yl)pentadecanoate 16. *Step 1.* A solution of **9** (53 mg, 0.10 mmol, >99:1 dr) in HCl (1.25 M in MeOH, 2 mL) was stirred at rt for 2 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (5 mL), and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), then dried, and concentrated *in vacuo* to give **13** as a white solid (40 mg).

Step 2. A solution of $4^{3,13}$ (26 mg, 0.10 mmol) in 1,2-dichloroethane (1 mL) was added to a stirred solution of the residue **13** from the previous step (40 mg) in 1,2-dichloroethane (1 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (40 mg, 0.19 mmol) were added, and the resultant mixture was stirred at rt for 16 h, before satd aq $NaHCO_3$ (5 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O/Et_3N, 40:59:1) gave **16** as a pale yellow oil (40 mg, 62%, >99:1 dr); $[\alpha]_D^{20}$ −14.5 (*c* 1.0, $CHCl_3$); ν_{max} 1735 (C═O); δ_H (400 MHz, C_6D_6) 1.10−1.76 (44H, m, C(4)H_2−C(14)H_2, C(2″)H_2−C(12″)H_2), 2.27 (4H, t, *J* 7.6, C(15)H_2, C(13″)H_2), 2.35−2.45 (1H, m, C(1″)H_A), 2.47−2.56 (1H, m, C(1″)H_B), 3.30 (3H, s, O*Me*), 3.44−3.52 (1H, m, C(3)*H*), 3.85 (1H, d, *J* 9.3, C(2)*H*), 6.74−6.78 (2H, m, C(5′)*H*, C(5‴)*H*), 7.00−7.10 (3H, m, C(4′)*H*, C(4‴)*H*, *p*-*Ph*), 7.12−7.17 (2H, m, *m*-*Ph*), 7.47−7.53 (2H, m, *o*-*Ph*), 8.47−8.52 (2H, m, C(6′)*H*, C(6‴)*H*), 8.54−8.60 (2H, m, C(2′)*H*, C(2‴)*H*); δ_C (100 MHz, C_6D_6) 26.2, 27.9, 29.8, 30.2, 30.3, 30.4, 30.5, 30.7, 31.2, 31.8, 33.0 (*C*(4)−*C*(14), *C*(2″)−*C*(12″)), 33.5 (*C*(15), *C*(13″)), 46.8 (*C*(1″)), 51.7 (O*Me*), 57.1 (*C*(2)), 60.9 (*C*(3)), 123.5 (*C*(5′), *C*(5‴)), 128.0, 129.2, 129.8 (*o*,*m*,*p*-*Ph*), 135.5 (*C*(4′), *C*(4‴)), 138.07, 138.09, 138.13 (*C*(3′), *C*(3‴), *i*-*Ph*), 148.2 (*C*(6′), *C*(6‴)), 151.0 (*C*(2′), *C*(2‴)), 173.8 (*C*(1)); *m*/*z* (ESI$^+$) 685 ([M + H]$^+$, 5%), 343 ([M+2H]$^{2+}$, 65%), 229 ([M + 3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{45}H_{70}N_3O_2^+$ ([M + H]$^+$) requires 684.5463; found 684.5468.

(2*S*,3*R*)-2-Phenyl-3-{*N*-[12″-(pyridin-3‴-yl)dodec-12″-yl]-amino}-15-(pyridin-3′-yl)pentadecanoic Acid [(−)-Nakinadine D] 17. A solution of **15** (22 mg, 0.033 mmol, >99:1 dr) in HCl (3.0 M aq, 1 mL) was stirred at 100 °C for 8 h and then concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I [100−200 mesh, OH^- form, eluent AcOH (2.0 M aq)], followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3), gave **17** as a colorless oil (13 mg, 60%, >99:1 dr); $[\alpha]_D^{20}$ −15.0 (*c* 1.0 in $CHCl_3$); ν_{max} 1575, 2853, 2924; δ_H (500 MHz, 127 mM in neutralized $CDCl_3$) 1.07−1.73 (42H, m, C(4)H_2−C(14)H_2, C(2″)H_2−C(11″)H_2), 2.58−2.62 (4H, m, *J* 7.7, C(15)H_2, C(12″)H_2), 2.67−2.75 (1H, m, C(1″)H_A), 2.77−2.89 (1H, m, C(1″)H_B), 3.10−3.17 (1H, m, C(3)*H*), 3.82 (1H, br d, *J* 2.8, C(2)*H*), 7.16−7.29 (5H, m, C(5′)*H*, C(5‴)*H*, *m*,*p*-*Ph*), 7.34 (2H, d, *J* 7.3, *o*-*Ph*), 7.47−7.49 (2H, m, C(4′)*H*, C(4‴)*H*), 8.34−8.54 (4H, m, C(2′)*H*, C(6′)*H*, C(2‴)*H*, C(6‴)*H*); δ_C (125 MHz, 127 mM in neutralized $CDCl_3$) 26.3, 26.9, 28.0, 28.7, 29.05, 29.07, 29.12, 29.22, 29.26, 29.29, 29.34, 29.36, 29.42, 29.44, 29.46, 29.47, 29.49, 29.51, 29.52, 29.7, 31.1 (*C*(4)−*C*(14),

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C(2″)−C(11″)), 33.0 (C(15), C(12″)), 45.7 (C(1″)), 51.7 (C(2)), 59.9 (C(3)), 123.3 (C(5′), C(5‴)), 127.5 (*p*-Ph), 128.7 (*m*-Ph), 129.6 (*o*-Ph), 135.3 (*i*-Ph), 135.8 (C(4′), C(4‴), 138.0 (C(3′), C(3‴), 147.0 (C(6′), C(6‴)), 149.8 (C(2′), C(2‴)), 175.1 (C(1)); *m*/*z* (ESI$^+$) 657 ([M + H]$^+$, 5%), 329 ([M+2H]$^{2+}$, 75%), 220 ([M + 3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{43}H_{66}N_3O_2^+$ ([M + H]$^+$) requires 656.5150; found 656.5123.

(2*S*,3*R*)-2-Phenyl-3-{*N*-[13″-(pyridin-3‴-yl)tridec-13″-yl]-amino)-15-(pyridin-3′-yl)pentadecanoic Acid [(−)-Nakinadine E] 18. A solution of **16** (40 mg, 0.06 mmol, >99:1 dr) in HCl (3.0 M aq, 2 mL) was stirred at 100 °C for 8 h and then concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I [100−200 mesh, OH$^-$ form, eluent AcOH (2.0 M aq)], followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3), gave **18** as a colorless oil (25 mg, 63%, >99:1 dr); $[\alpha]_D^{20}$ −15.2 (*c* 1.0 in $CHCl_3$); ν_{max} 1574, 1651, 2851, 2921; δ_H (500 MHz, 127 mM in neutralized $CDCl_3$) 1.07−1.69 (44H, m, C(4)H_2−C(14)H_2, C(2″)H_2−C(12″)H_2), 2.58−2.62 (4H, m, C(15)H_2, C(13″)H_2), 2.66−2.74 (1H, m, C(1″)H_A), 2.78−2.89 (1H, m, C(1″)H_B), 3.10−3.18 (1H, m, C(3)*H*), 3.84 (1H, br d, *J* 2.8, C(2)*H*), 7.16−7.28 (5H, m, C(5′)*H*, C(5‴)*H*, *m*,*p*-Ph), 7.35 (2H, d, *J* 7.3, *o*-Ph), 7.48−7.50 (2H, m, C(4′)*H*, C(4‴)*H*), 8.31−8.54 (4H, m, C(2′)*H*, C(6′)*H*, C(2‴)*H*, C(6‴)*H*); δ_C (125 MHz, 127 mM in neutralized $CDCl_3$) 26.3, 26.9, 27.5, 28.5, 29.09, 29.12, 29.13, 29.23, 29.28, 29.36, 29.39, 29.48, 29.53, 29.6, 31.1 (C(4)−C(14), C(2″)−C(12″)), 33.0 (C(15), C(13″), 45.5 (C(1″)), 51.9 (C(2)), 59.9 (C(3)), 123.2 (C(5′), C(5‴)), 127.4 (*p*-Ph), 128.6 (*m*-Ph), 129.6 (*o*-Ph), 135.6 (*i*-Ph), 135.8 (C(4′), C(4‴)), 138.0 (C(3′), C(3‴), 147.1 (C(6′), C(6‴)), 149.9 (C(2′), C(2‴)), 175.6 (C(1)); *m*/*z* (ESI$^+$) 671 ([M + H]$^+$, 5%), 336 ([M + 2H]$^{2+}$, 65%), 224 ([M + 3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{44}H_{68}N_3O_2^+$ ([M + H]$^+$) requires 670.5306; found 670.5282.

Methyl (2*R*,3*R*)-2-Phenyl-3-{*N*-[12″-(pyridin-3‴-yl)dodecyl]-amino}-15-(pyridin-3′-yl)pentadecanoate 19. *Step 1.* A solution of **10** (180 mg, 0.34 mmol, 98:2 dr) in HCl (1.25 M in MeOH, 4 mL) was stirred at rt for 2 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (10 mL), and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 10 mL), then dried, and concentrated *in vacuo* to give **14** as a white solid (144 mg).

Step 2. A solution of **3**[13] (89 mg, 0.34 mmol) in 1,2-dichloroethane (4 mL) was added to a stirred solution of the residue **14** from the previous step (144 mg) in 1,2-dichloroethane (4 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (144 mg, 0.68 mmol) were added, and the resultant mixture was stirred at rt for 16 h, before satd aq $NaHCO_3$ (10 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **19** as a pale yellow oil (150 mg, 66% from **10**, 98:2 dr); $[\alpha]_D^{20}$ +10.0 (*c* 1.0 in $CHCl_3$); ν_{max} 1735 (C═O); δ_H (500 MHz, C_6D_6) 0.97−1.56 (42H, m, C(4)H_2−C(14)H_2, C(2″)H_2−C(11″)H_2), 2.22−2.31 (4H, m, C(15)H_2, C(12″)H_2), 2.66−2.81 (2H, m, C(1″)H_2), 3.37 (3H, s, O*Me*), 3.44−3.51 (1H, m, C(3)*H*), 3.75 (1H, d, *J* 9.8, C(2)*H*), 6.74−6.78 (2H, m, C(5′)*H*, C(5‴)*H*), 6.98−7.08 (3H, m, C(4′)*H*, C(4‴)*H*, *p*-Ph), 7.11−7.17 (2H, m, *m*-Ph), 7.44−7.49 (2H, m, *o*-Ph), 8.46−8.52 (2H, m, C(6′)*H*, C(6‴)*H*), 8.55−8.65 (2H, m, C(2′)*H*, C(2‴)*H*); δ_C (125 MHz, C_6D_6) 25.5, 28.2, 29.8, 30.17, 30.19, 30.35, 30.37, 30.43, 30.45, 30.48, 30.51, 30.6, 31.5, 31.7, 31.8 (C(4)−C(14), C(2″)−C(11″)), 33.5 (C(15), C(12″), 47.3 (C(1″)), 51.7 (O*Me*), 58.2 (C(2)), 61.0 (C(3)), 123.5 (C(5′), C(5‴)), 128.0 (*p*-Ph), 129.2, 129.5 (*o*,*m*-Ph), 135.5 (C(4′), C(4‴)), 138.07, 138.09, 138.4 (C(3′), C(3‴), *i*-Ph), 148.2 (C(6′), C(6‴)), 151.0 (C(2′), C(2‴)), 174.3 (C(1)); *m*/*z* (ESI$^+$) 671 ([M + H]$^+$, 5%), 336 ([M + 2H]$^{2+}$, 100%), 224 ([M + 3H]$^{3+}$, 90%); HRMS (ESI$^+$) $C_{44}H_{68}N_3O_2^+$ ([M + H]$^+$) requires 670.5306; found 670.5300.

Methyl (2*R*,3*R*)-2-Phenyl-3-{*N*-[13″-(pyridin-3‴-yl)tridecyl]-amino}-15-(pyridin-3′-yl)pentadecanoate 20. *Step 1.* A solution of **10** (157 mg, 0.30 mmol, 98:2 dr) in HCl (1.25 M in MeOH, 5 mL) was stirred at rt for 2 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (10 mL), and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 10 mL), then dried, and concentrated *in vacuo* to give **14** as a white solid (120 mg).

Step 2. A solution of **4**[3,13] (82 mg, 0.28 mmol) in 1,2-dichloroethane (3 mL) was added to a stirred solution of the residue **14** from the previous step (120 mg) in 1,2-dichloroethane (3 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (118 mg, 0.56 mmol) were added, and the resultant mixture was stirred at rt for 16 h, before satd aq $NaHCO_3$ (10 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O/Et_3N, 40:59:1) gave **20** as a pale yellow oil (128 mg, 63% from **10**, 98:2 dr); $[\alpha]_D^{20}$ +22.0 (*c* 1.0, $CHCl_3$); ν_{max} 1736 (C═O); δ_H (400 MHz, C_6D_6) 1.08−1.55 (44H, m, C(4)H_2−C(14)H_2, C(2″)H_2−C(12″)H_2), 2.25−2.27 (4H, m, C(15)H_2, C(13″)H_2), 2.65−2.83 (2H, m, C(1″)H_2), 3.37 (3H, s, O*Me*), 3.44−3.52 (1H, m, C(3)*H*), 3.76 (1H, d, *J* 9.8, C(2)*H*), 6.74−6.78 (2H, m, C(5′)*H*, C(5‴)*H*), 6.99−7.09 (3H, m, C(4′)*H*, C(4‴)*H*, *p*-Ph), 7.12−7.19 (2H, m, *m*-Ph), 7.44−7.50 (2H, m, *o*-Ph), 8.47−8.53 (2H, m, C(6′)*H*, C(6‴)*H*), 8.54−8.60 (2H, m, C(2′)*H*, C(2‴)*H*); δ_C (100 MHz, C_6D_6) 25.5, 28.2, 29.8, 30.17, 30.19, 30.33, 30.35, 30.38, 30.44, 30.48, 30.53, 30.6, 31.5, 31.7, 31.8 (C(4)−C(14), C(2″)−C(12″)), 33.5 (C(15), C(13″), 47.3 (C(1″)), 51.7 (O*Me*), 58.2 (C(2)), 61.0 (C(3)), 123.5 (C(5′), C(5‴)), 128.0 (*p*-Ph), 129.2, 129.5 (*o*,*m*-Ph), 135.5 (C(4′), C(4‴)), 138.1, 138.4 (C(3′), C(3‴), *i*-Ph), 148.2 (C(6′), C(6‴)), 151.1 (C(2′), C(2‴)), 174.2 (C(1)); *m*/*z* (ESI$^+$) 685 ([M + H]$^+$, 5%), 343 ([M + 2H]$^{2+}$, 65%), 229 ([M + 3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{45}H_{70}N_3O_2^+$ ([M + H]$^+$) requires 684.5463; found 684.5459.

(2*R*,3*R*)-2-Phenyl-3-{*N*-[12″-(pyridin-3‴-yl)dodec-12″-yl]-amino}-15-(pyridin-3′-yl)pentadecanoic Acid 21 [(+)-2-*epi*-Nakinadine D]. A solution of **19** (100 mg, 0.15 mmol, 98:2 dr) in HCl (3.0 M aq, 5 mL) was stirred at 100 °C for 8 h and then concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I [100−200 mesh, OH$^-$ form, eluent AcOH (2.0 M aq)], followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3), gave **21** as a colorless oil (59 mg, 60%, 98:2 dr); $[\alpha]_D^{20}$ +8.0 (*c* 1.0 in $CHCl_3$); ν_{max} 1574, 1596, 2852, 2922; δ_H (500 MHz, 127 mM in neutralized $CDCl_3$) 1.03−1.41 (34H, m, C(5)H_2−C(13)H_2, C(3″)H_2−C(10″)H_2), 1.46−1.54 (2H, m, C(4)H_2), 1.57−1.67 (4H, m, C(14)H_2, C(11″)H_2), 1.69−1.80 (2H, m, C(2″)H_2), 2.55−2.67 (5H, m, C(15)H_2, C(1″)H_A, C(12″)H_2), 2.81−2.94 (1H, m, C(1″)H_B), 3.31−3.39 (1H, m, C(3)*H*), 3.67−3.75 (1H, m, C(2)*H*), 7.16−7.25 (3H, m, C(5′)*H*, C(5‴)*H*, *p*-Ph), 7.27−7.35 (4H, m, *o*,*m*-Ph), 7.46−7.52 (2H, m, C(4′)*H*, C(4‴)*H*), 8.43−8.47 (4H, m, C(2′)*H*, C(6′)*H*, C(2‴)*H*, C(6‴)*H*); δ_C (125 MHz, 127 mM in neutralized $CDCl_3$) 24.9, 26.75, 26.81, 28.8, 29.10, 29.13, 29.35, 29.38, 29.40, 29.46, 29.48, 29.51, 29.53, 29.56 (C(4)−C(13), C(2″)−C(10″)), 31.1 (C(14), C(11″)), 33.0 (C(15), C(12″)), 44.6 (C(1″)), 54.3 (C(2)), 60.8 (C(3)), 123.2 (C(5′), C(5‴)), 127.0 (*p*-Ph), 128.5 (*m*-Ph), 128.7 (*o*-Ph), 135.7 (C(4′), C(4‴)), 137.9 (C(3′), C(3‴)), 139.1 (*i*-Ph), 147.1 (C(6′), C(6‴)), 149.9 (C(2′), C(2‴)), 176.7 (C(1)); *m*/*z* (ESI$^+$) 657 ([M + H]$^+$, 5%), 329 ([M + 2H]$^{2+}$, 75%), 220 ([M + 3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{43}H_{65}N_3NaO_2^+$ ([M + Na]$^+$) requires 678.4969; found 678.4942.

(2*R*,3*R*)-2-Phenyl-3-{*N*-[13″-(pyridin-3‴-yl)tridec-13″-yl]-amino}-15-(pyridin-3′-yl)pentadecanoic Acid 22 [(+)-2-*epi*-Nakinadine E]. A solution of **20** (80 mg, 0.12 mmol, 98:2 dr) in HCl (3.0 M aq, 4 mL) was stirred at 100 °C for 8 h and then concentrated *in vacuo*. Purification via ion exchange chromatography on Amberlite CG-400 [100−200 mesh, OH$^-$ form, eluent AcOH (2.0 M aq)], followed by flash column chromatography (eluent $CHCl_3$/MeOH, 95:5), gave **22** as a colorless oil (48 mg, 61%, 98:2 dr); $[\alpha]_D^{20}$ +8.4 (*c* 1.0 in $CHCl_3$); ν_{max} 1573, 1652, 2849, 2919; δ_H (500 MHz, 127 mM in neutralized $CDCl_3$) 1.02−1.80 (44H, m, C(4)H_2−C(14)H_2, C(2″)H_2−C(12″)H_2), 2.54−2.64 (5H, m, C(15)H_2, C(13″)H_2, C(1″)H_A), 2.81−2.93 (1H, m, C(1″)H_B), 3.28−3.40 (1H, m, C(3)*H*), 3.64−3.76 (1H, m, C(2)*H*), 7.11−7.25 (3H, m, C(5′)*H*, C(5‴)*H*, *p*-Ph), 7.26−7.34 (4H, m, *o*,*m*-Ph), 7.47−7.51 (2H, m, C(4′)*H*, C(4‴)*H*), 8.25−8.69 (4H, m, C(2′)*H*, C(6′)*H*, C(2‴)*H*,

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C(6‴)*H*); δ_C (125 MHz, 127 mM in neutralized $CDCl_3$) 25.0, 26.7, 26.8, 28.8, 29.10, 29.13, 29.3, 29.38, 29.39, 29.47, 29.51, 29.54, 29.58, 29.60, 31.1 (*C*(4)−*C*(14), *C*(2″)−*C*(12″)), 33.0 (*C*(15), *C*(13″), 44.6 (*C*(1″)), 54.2 (*C*(2)), 60.8 (*C*(3)), 123.3 (*C*(5′), *C*(5‴)), 127.0 (*p-Ph*), 128.5 (*m-Ph*), 128.7 (*o-Ph*), 135.7 (*C*(4′), *C*(4‴)), 138.0 (*C*(3′), *C*(3‴), 139.0 (*i-Ph*), 147.1 (*C*(6′), *C*(6‴)), 149.9 (*C*(2′), *C*(2‴)), 176.7 (*C*(1)); *m/z* (ESI$^+$) 671 ([M + H]$^+$, 5%), 336 ([M + 2H]$^{2+}$, 65%), 224 ([M + 3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{44}H_{67}N_3NaO_2^+$ ([M + Na]$^+$) requires 692.5125; found 692.5121.

Methyl (2*S*,3*R*,13*Z*,11″*Z*)-2-Phenyl-3-{*N*-[14″-(pyridin-3‴-yl)-tetradec-11″-enyl]amino}-16-(pyridin-3′-yl)hexadec-13-enoate 26. *Step 1.* A solution of **23**[5] (297 mg, 0.55 mmol, 97:3 dr [(*Z*):(*E*) ratio]) in HCl (1.25 M in MeOH, 4 mL) was stirred at rt for 2 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL), and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), dried, and concentrated *in vacuo* to give **25** as a white solid (239 mg).

Step 2. A solution of **5**[4,5,13] (159 mg, 0.55 mmol, 97:3 dr [(*Z*):(*E*) ratio]) in 1,2-dichloroethane (4 mL) was added to a stirred solution of the residue **25** from the previous step (239 mg) in 1,2-dichloroethane (4 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (235 mg, 1.11 mmol) were added, and the resultant mixture was stirred at rt for 16 h, before satd aq $NaHCO_3$ (10 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **26** as a pale yellow oil (233 mg, 60% from **23**, ∼95% diastereoisomeric purity);[18] $[\alpha]_D^{20}$ −17.0 (*c* 1.0 in $CHCl_3$); ν_{max} 1734 (C═O); δ_H (500 MHz, C_6D_6) 1.10−1.75 (32H, m, C(4)H_2−C(11)H_2, C(2″)H_2−C(9″)H_2), 1.85−1.95 (4H, m, C(12)H_2, C(10″)H_2), 2.14−2.21 (4H, m, C(15)H_2, C(13″)H_2), 2.29−2.44 (5H, m, C(16)H_2, C(14″)H_2, C(1″)H_A), 2.47−2.56 (1H, m, C(1″)H_B), 3.30 (3H, s, O*Me*), 3.45−3.52 (1H, m, C(3)*H*), 3.85 (1H, d, *J* 9.1, C(2)*H*), 5.26−5.35 (2H, m, C(14)*H*, C(12″)H_2), 5.38−5.46 (2H, m, C(13)*H*, C(11″)H_2), 6.71−6.79 (2H, m, C(5′)*H*, C(5‴)*H*), 6.98−7.10 (3H, m, C(4′)*H*, C(4‴)*H*, *p-Ph*), 7.12−7.19 (2H, m, *m-Ph*), 7.48−7.53 (2H, m, *o-Ph*), 8.45−8.59 (4H, m, C(2′)*H*, C(6′)*H*, C(2‴)*H*, C(6‴)*H*); δ_C (125 MHz, C_6D_6) 26.2, 27.9, 29.4, 30.0, 30.26, 30.32, 30.34, 30.38, 30.42, 30.5, 30.7, 31.2 (*C*(5)−*C*(12), *C*(15), *C*(2″)−*C*(10″), *C*(13″)), 33.0 (*C*(4)), 33.5 (*C*(16), *C*(14″)), 46.8 (*C*(1″)), 51.7 (O*Me*), 57.1 (*C*(2)), 60.9 (*C*(3)), 123.5 (*C*(5′), *C*(5‴)), 128.0 (*p-Ph*), 128.8 (*C*(14), *C*(12″)), 129.2, 129.8 (*o,m-Ph*), 131.71, 131.73 (*C*(13), *C*(11″)), 135.7 (*C*(4′), *C*(4‴)), 137.4, 138.1 (*C*(3′), *C*(3‴), *i-Ph*), 148.3 (*C*(6′), *C*(6‴)), 151.1 (*C*(2′), *C*(2‴)), 173.8 (*C*(1)); *m/z* (ESI$^+$) 709 ([M + H]$^+$, 5%), 355 ([M + 2H]$^{2+}$, 50%), 237 ([M + 3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{47}H_{70}N_3O_2^+$ ([M + H]$^+$) requires 708.5463; found 708.5468.

(2*S*,3*R*,13*Z*,11″*Z*)-2-Phenyl-3-{*N*-[14″-(pyridin-3‴-yl)tetradec-11″-enyl]amino}-16-(pyridin-3′-yl)hexadec-13-enoic Acid [(−)-Nakinadine F] 27. A solution of **26** (60 mg, 0.085 mmol, ∼95% diastereoisomeric purity)[18] in HCl (3.0 M aq, 2 mL) was stirred at 70 °C for 80 h and then concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I [100−200 mesh, OH^- form, eluent AcOH (2.0 M, aq)], followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3), gave **27** as a colorless oil (33 mg, 56%, ∼95% diastereoisomeric purity);[18] $[\alpha]_D^{20}$ −15.1 (*c* 1.0 in $CHCl_3$); ν_{max} 1575, 1594, 2853, 2924; δ_H (500 MHz, 127 mM in neutralized $CDCl_3$) 1.12−1.71 (32H, C(4)H_2−C(11)H_2, C(2″)H_2−C(9″)H_2), 1.85−2.00 (4H, m, C(12)H_2, C(10″)H_2), 2.29−2.41 (4H, m, C(15)H_2, C(13″)H_2), 2.60−2.77 (5H, m, C(16)H_2, C(1″)H_A, C(14″)H_2), 2.78−2.86 (1H, m, C(1″)H_B), 3.05−3.16 (1H, m, C(3)*H*), 3.80−3.88 (1H, m, C(2)*H*), 5.33−5.44 (4H, m, C(13)*H*, C(14)*H*, C(11″)H_2, C(12″)H_2), 7.19−7.29 (3H, m, C(5′)*H*, C(5‴)*H*, *m,p-Ph*), 7.31−7.37 (2H, m, *o-Ph*), 7.48−7.52 (2H, m, C(4′)*H*, C(4‴)*H*), 8.35−8.51 (4H, m, C(2′)*H*, C(6′)*H*, C(2‴)*H*, C(6‴)*H*); δ_C (125 MHz, 127 mM in neutralized $CDCl_3$) 26.3, 26.9, 27.14, 27.17, 27.9, 28.8, 29.12, 29.20, 29.22, 29.28, 29.37, 29.38, 29.45, 29.48, 29.49, 29.7 (*C*(4)−*C*(12), *C*(15), *C*(2″)−*C*(10″), *C*(13″)), 33.0 (*C*(16), *C*(14″)), 45.8 (*C*(1″)), 51.9 (*C*(2)), 60.0 (*C*(3)), 123.2 (*C*(5′), *C*(5‴)), 127.4 (*p-Ph*), 127.7 (*C*(14), *C*(12″)), 128.6, 129.6 (*o,m-Ph*), 131.4 (*C*(13), *C*(11″)), 135.5 (*i-Ph*), 135.97, 136.04 (*C*(4′), *C*(4‴)), 137.3 (*C*(3′), *C*(3‴)), 147.1, 147.2 (*C*(6′), *C*(6‴)), 149.8, 149.9 (*C*(2′), *C*(2‴)), 175.3 (*C*(1)); *m/z* (ESI$^+$) 695 ([M + H]$^+$, 5%), 348 ([M + 2H]$^{2+}$, 40%), 232 ([M + 3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{46}H_{68}N_3O_2^+$ ([M + H]$^+$) requires 694.5306; found 694.5299.

Methyl (2*R*,3*R*,13*Z*,11″*Z*)-2-Phenyl-3-{*N*-[14″-(pyridin-3‴-yl)-tetradec-11″-enyl]amino}-16-(pyridin-3′-yl)hexadec-13-enoate 30. *Step 1.* A solution of **24**[5] (170 mg, 0.32 mmol, 94% diastereoisomeric purity)[18] in HCl (1.25 M in MeOH, 4 mL) was stirred at rt for 2 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL), and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), dried, and concentrated *in vacuo* to give **29** as a white solid (137 mg).

Step 2. A solution of **5**[4,5,13] (90 mg, 0.32 mmol, 97:3 dr [(*Z*):(*E*) ratio]) in 1,2-dichloroethane (4 mL) was added to a stirred solution of the residue **29** from the previous step (137 mg) in 1,2-dichloroethane (4 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (133 mg, 0.63 mmol) were added, and the resultant mixture was stirred at rt for 16 h, before satd aq $NaHCO_3$ (10 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **30** as a pale yellow oil (129 mg, 58% from **24**, ∼93% diastereoisomeric purity);[18] $[\alpha]_D^{20}$ −17.0 (*c* 1.0 in $CHCl_3$); ν_{max} 1735 (C═O); δ_H (500 MHz, C_6D_6) 1.04−1.58 (32H, m, C(4)H_2−C(11)H_2, C(2″)H_2−C(9″)H_2), 1.85−1.96 (4H, m, C(12)H_2, C(10″)H_2), 2.13−2.21 (4H, m, C(15)H_2, C(13″)H_2), 2.29−2.37 (4H, m, C(16)H_2, C(14″)H_2) 2.66−2.82 (2H, m, C(1″)H_2), 3.37 (3H, s, O*Me*), 3.44−3.52 (1H, m, C(3)*H*), 3.76 (1H, d, *J* 10.1, C(2)*H*), 5.26−5.34 (2H, m, C(14)*H*, C(12″)H_2), 5.38−5.46 (2H, m, C(13)*H*, C(11″)H_2), 6.72−6.78 (2H, m, C(5′)*H*, C(5‴)*H*), 6.98−7.09 (3H, m, C(4′)*H*, C(4‴)*H*, *p-Ph*), 7.13−7.19 (2H, m, *m-Ph*), 7.45−7.49 (2H, m, *o-Ph*), 8.44−8.62 (4H, m, C(2′)*H*, C(6′)*H*, C(2‴)*H*, C(6‴)*H*); δ_C (125 MHz, C_6D_6) 25.5, 27.91, 27.93, 28.1, 29.4, 29.98, 30.03, 30.28, 30.30, 30.33, 30.36, 30.43, 30.45, 30.53, 30.7, 31.5, 31.7 (*C*(4)−*C*(12), *C*(15), *C*(2″)−*C*(10″), *C*(13″)), 33.5 (*C*(16), *C*(14″)), 47.3 (*C*(1″)), 51.7 (O*Me*), 58.2 (*C*(2)), 61.0 (*C*(3)), 123.5 (*C*(5′), *C*(5‴)), 128.0 (*p-Ph*), 128.8 (*C*(14), *C*(12″)), 129.2, 129.5 (*o,m-Ph*), 131.70, 131.72 (*C*(13), *C*(11″)), 135.7 (*C*(4′), *C*(4‴)), 137.4, 138.4 (*C*(3′), *C*(3‴), *i-Ph*), 148.3 (*C*(6′), *C*(6‴)), 151.1 (*C*(2′), *C*(2‴)), 174.3 (*C*(1)); *m/z* (ESI$^+$) 709 ([M + H]$^+$, 5%), 355 ([M + 2H]$^{2+}$, 50%), 237 ([M + 3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{47}H_{70}N_3O_2^+$ ([M + H]$^+$) requires 708.5463; found 708.5445.

(2*R*,3*R*,13*Z*,11″*Z*)-2-Phenyl-3-{*N*-[14″-(pyridin-3‴-yl)tetradec-11″-enyl]amino}-16-(pyridin-3′-yl)hexadec-13-enoic Acid 31 [(+)-2-*epi*-Nakinadine F]. A solution of **30** (60 mg, 0.085 mmol, ∼93% diastereoisomeric purity)[18] in HCl (3.0 M aq, 2 mL) was stirred at 70 °C for 80 h and then concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I (100−200 mesh, OH^- form, eluent AcOH (2.0 M aq)], followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3), gave **31** as a colorless oil (34 mg, 58%, ∼93% diastereoisomeric purity);[18] $[\alpha]_D^{20}$ +8.1 (*c* 1.0 in $CHCl_3$); ν_{max} 1576, 1599, 2853, 2924; δ_H (500 MHz, 127 mM in neutralized $CDCl_3$) 1.03−1.81 (32H, C(4)H_2−C(11)H_2, C(2″)H_2−C(9″)H_2), 1.86−1.98 (4H, m, C(12)H_2, C(10″)H_2), 2.31−2.40 (4H, m, C(15)H_2, C(13″)H_2), 2.57−2.71 (5H, m, C(16)H_2, C(1″)H_A, C(14″)H_2), 2.88−2.94 (1H, m, C(1″)H_B), 3.30−3.41 (1H, m, C(3)*H*), 3.72 (1H, d, *J* 8.8, C(2)*H*), 5.32−5.46 (4H, m, C(13)*H*, C(14)*H*, C(11″)H_2, C(12″)H_2), 7.16−7.25 (3H, m, C(5′)*H*, C(5‴)*H*, *p-Ph*), 7.26−7.35 (4H, m, *o,m-Ph*), 7.47−7.54 (2H, m, C(4′)*H*, C(4‴)*H*), 8.36−8.50 (4H, m, C(2′)*H*, C(6′)*H*, C(2‴)*H*, C(6‴)*H*); δ_C (125 MHz, 127 mM in neutralized $CDCl_3$) 24.7, 26.8, 27.18, 27.20, 28.7, 29.1, 29.2, 29.3, 29.36, 29.40, 29.43, 29.47, 29.49, 29.50, 29.53, 29.7 (*C*(4)−*C*(12), *C*(15), *C*(2″)−*C*(10″), *C*(13″)), 33.0 (*C*(16), *C*(14″)), 44.8 (*C*(1″)), 54.4 (*C*(2)), 60.7 (*C*(3)), 123.2 (*C*(5′), *C*(5‴)), 127.1 (*p-Ph*), 127.7 (*C*(14), *C*(12″)), 128.5, 128.8 (*o,m-Ph*), 131.4 (*C*(13), *C*(11″)), 135.9 (*C*(4′), *C*(4‴)), 137.2 (*C*(3′), *C*(3‴)), 138.9 (*i-Ph*), 147.3 (*C*(6′), *C*(6‴)), 150.0 (*C*(2′), *C*(2‴)), 176.7

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(C(1)); *m/z* (ESI$^+$) 695 ([M + H]$^+$, 5%), 348 ([M + 2H]$^{2+}$, 40%), 232 ([M + 3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{46}H_{68}N_3O_2^+$ ([M + H]$^+$) requires 694.5306; found 694.5290.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra, and crystallographic information file (for structure CCDC 1026027). 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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(16) A sample of **24** was also isolated from this reaction, in 10% yield and 94:3:3 dr [(2*R*,3*R*,R_S,*Z*):(2*R*,3*R*,R_S,*E*):(2*S*,3*R*,R_S,*Z*) ratio], i.e., 94% diastereoisomeric purity.

(17) A sample of **23** was also isolated from this reaction, in 9% yield and 97:3 dr [(*Z*):(*E*) ratio].

(18) Diastereoisomeric purity is the percentage of major diastereoisomer in the sample.

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