

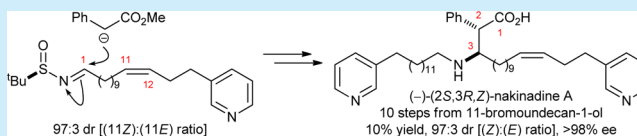
(–)-(2*S*,3*R*,*Z*)-Nakinadine A: First Asymmetric Synthesis and Absolute Configuration Assignment

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S Supporting Information

ABSTRACT: Mannich-type reaction of methyl phenylacetate with the *N*-*tert*-butylsulfinyl imine derived from (*R*)-*tert*-butylsulfinamide and (*Z*)-14-(pyridin-3'-yl)tetradec-11-enal has been used as the key step in the first asymmetric synthesis of (–)-nakinadine A. Both the 2,3-*syn*- and 2,3-*anti*-diastereoisomers were prepared; comparison of spectroscopic and specific rotation data facilitated assignment of the absolute (2*S*,3*R*,*Z*)-configuration within the natural product. (–)-(2*S*,3*R*,*Z*)-Nakinadine A was prepared in 10 steps from 11-bromoundecan-1-ol, in 10% overall yield, 97:3 dr [(*Z*):(*E*) ratio], and >98% ee.



In 2007 and 2008, Kobayashi et al. reported the isolation of the nakinadine family of alkaloids from the Okinawan sponge *Amphimedon* sp.^{1,2} Six members of the family were identified (nakinadines A–F), the common structural features of which are an α -phenyl- β -amino acid moiety with a long-chain aliphatic *N*-substituent capped by a pyridin-3-yl group (Figure 1). As nakinadines A and D–F possess a similar long-chain aliphatic substituent at the β -position, these members of this alkaloid family can exist as one of four possible stereoisomers (two pairs of enantiomers in each case, excluding the possibility for geometric isomerism in nakinadines A and F). Kobayashi et al. proposed their relative (*RS*,*SR*)-configurations on the basis of ¹H–¹³C coupling constant analysis, but of all the nakinadine alkaloids a specific rotation value for only nakinadine A was reported {[α]_D²³ –3 (c 1.0 in CHCl₃)},¹ making this alkaloid a palpable target for asymmetric synthesis to establish its absolute configuration. To date, we have reported the only syntheses of any of these alkaloids: the asymmetric syntheses of nakinadines B³ and C⁴ were achieved via a common strategy using the conjugate addition of LiNBn₂ to an *N*- α -phenylacryloyl SuperQuat derivative with diastereoselective enolate protonation as the key step;⁵ reductive *N*-alkylation was then employed to introduce the requisite long-chain aliphatic substituent.^{3,4} In continuation of our investigations within this area, we delineate herein the first asymmetric synthesis of the (2*S*,3*R*,*Z*)- and (2*R*,3*R*,*Z*)-stereoisomers of nakinadine A and, through comparison of spectroscopic and specific rotation data, assign the absolute (2*S*,3*R*,*Z*)-configuration within natural (–)-nakinadine A.

Diastereoselective nucleophilic addition to an enantiopure *N*-*tert*-butylsulfinyl imine (derived from condensation of enantiopure *tert*-butylsulfinamide 4⁶ with the corresponding aldehyde or ketone) has emerged as a powerful method for the asymmetric synthesis of a range of amines⁷ owing to the wide range of nucleophiles, including organometallic reagents,⁸

cyanide (Strecker-type reaction),⁹ and ester enolates (Mannich-type reaction),¹⁰ that participate in this reaction manifold.⁷ We envisaged that Mannich-type reaction of methyl phenylacetate with *N*-*tert*-butylsulfinyl imine 5 [derived from condensation of aldehyde 3 with (*R*)-4] would facilitate the synthesis of the diastereoisomers of nakinadine A. Thus, 11-bromoundecan-1-ol 1 was elaborated to alcohol 2 in four steps via our previously reported approach,⁴ in 53% overall yield and 97:3 dr [(*Z*):(*E*) ratio],¹¹ and oxidation of 2 with IBX in EtOAc¹² gave the requisite aldehyde 3. Condensation of 3 with (*R*)-4 (>98% ee) gave *N*-*tert*-butylsulfinyl imine 5 in 80% yield (from 2) and 97:3 dr [(11*Z*):(11*E*) ratio],¹¹ indicating that formation of the imine functionality had occurred with complete (*E*)-selectivity⁷ (Scheme 1).

Treatment of methyl phenylacetate with LiHMDS gave an 85:15 mixture of the corresponding (*E*)- and (*Z*)-enolates,¹³ and reaction with imine 5 in the presence of MgBr₂ gave an approximate 80:20 mixture of α -phenyl- β -sulfinamido esters 7 and 8.¹⁴ In a separate experiment, use of MeMgBr as the base under analogous conditions gave a similar, approximate 80:20 mixture of 7 and 8. Although the ratio of the diastereoisomeric enolates could not be determined in the magnesium case,¹³ a similar ratio to that obtained using LiHMDS may be assumed, based upon the similar diastereoselectivities elicited by both of these Mannich-type reactions. Purification of the crude reaction mixture allowed isolation of 7 in 60% yield and 97:3 dr [(*Z*):(*E*) ratio].¹¹ Hydrogenation of this sample of 7 gave 9 as a single diastereoisomer (>99:1 dr), thus unambiguously establishing that the 97:3 dr of 7 represents the ratio of geometric olefin isomers, consistent with the ratio of geometric isomers of 5 (Scheme 2). Furthermore, the relative configuration within 9 was unambiguously established by single

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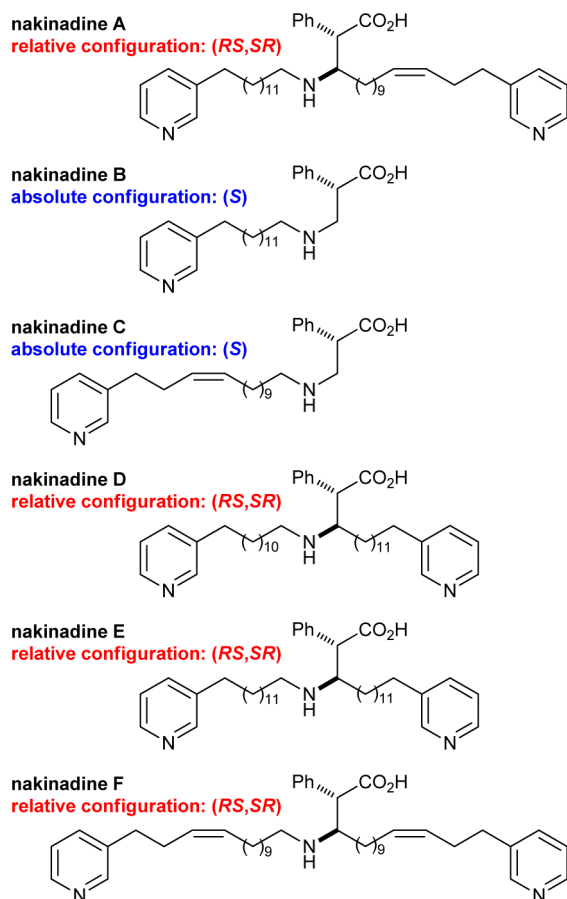
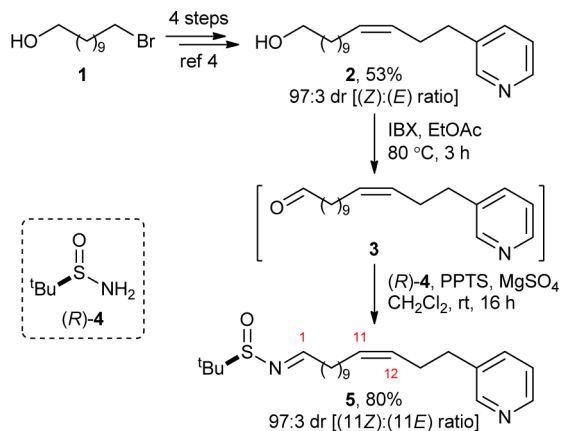


Figure 1. Reported structures and assigned relative and absolute configurations of the nakinadine alkaloids.

Scheme 1



crystal X-ray diffraction analysis,^{15,16} with its absolute (*2R*,*3S*,*R_S*)-configuration following from the known (*R*)-configuration of the sulfur atom (Figure 2). Thus, the absolute (*2R*,*3S*,*R_S*,*Z*)-configuration within 7 was also unambiguously assigned. The formation of 7 as the major diastereoisomer from this asymmetric Mannich-type reaction is entirely consistent with the reaction proceeding via a chairlike transition state 6, which has previously been proposed to rationalize the diastereoselectivity of this class of reaction;^{7,10} the facial selectivity for attack on the *N*-*tert*-butylsulfinyl imine may be determined either by chelation or sterics (orientation of the *S*-lone pair toward the approaching enolate). Repetition of this

Scheme 2

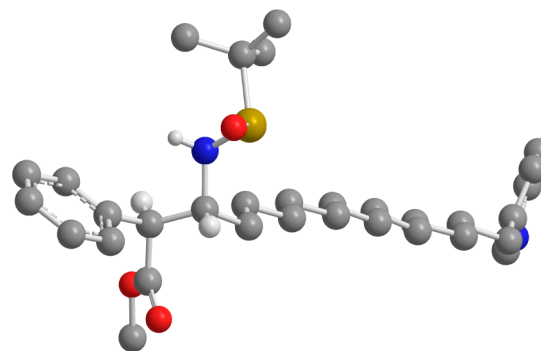
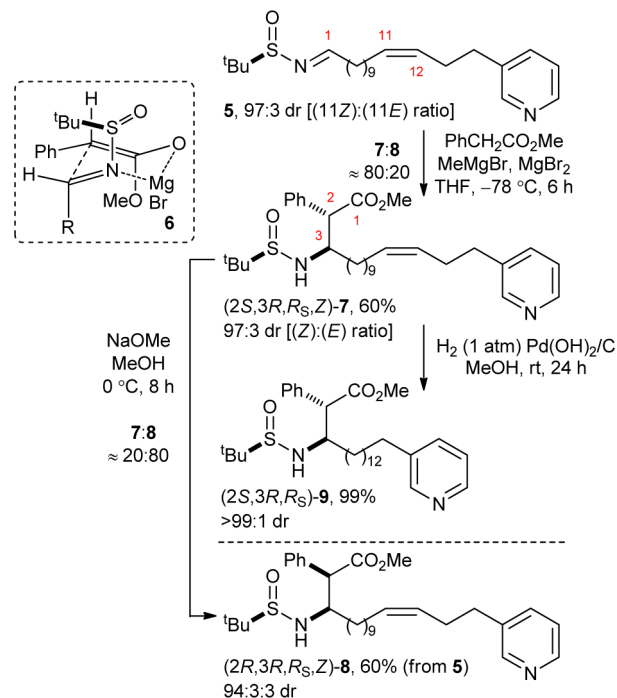


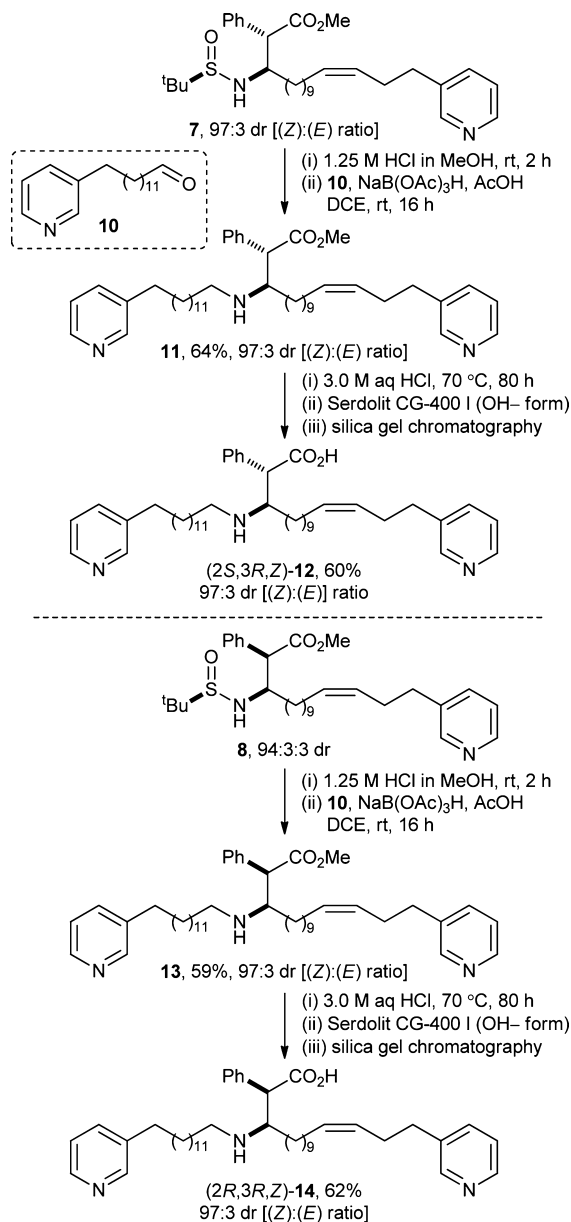
Figure 2. X-ray crystal structure of (*2S*,*3R*,*R_S*)-9 (selected H atoms are omitted for clarity).

experiment and treatment of the crude reaction mixture (approximate 80:20 mixture of 7 and 8, respectively) with NaOMe in MeOH at 0 °C for 8 h resulted in formation of an approximate 20:80 mixture of 7 and 8, respectively, showing that 7 and 8 are related as epimers at C(2) and, hence, establishing the absolute (*2R*,*3R*,*R_S*,*Z*)-configuration within 8. Purification gave a sample of 8 in 60% isolated yield (from 5) and 94:3:3 dr [(*2R*,*3R*,*R_S*,*Z*):(*2R*,*3R*,*R_S*,*E*):(*2S*,*3R*,*R_S*,*Z*)]¹⁷ (Scheme 2).

Treatment of 7 (97:3 dr [(*Z*):(*E*) ratio]) with HCl in MeOH effected hydrolysis of the *N*-*tert*-butylsulfinyl group to give the corresponding primary amine and was followed by reductive *N*-alkylation using 13-(pyridin-3'-yl)tridecanol 10³ in the presence of NaB(OAc)₃H to give secondary amine 11 in 64% yield (from 7) and 97:3 dr [(*Z*):(*E*) ratio].¹¹ Finally, hydrolysis of 11 upon treatment with 3.0 M aq HCl at 70 °C¹⁸ followed by sequential purification on Serdolit CG-400 I resin (OH⁻ form) and silica gel gave (*2S*,*3R*,*Z*)-12 in 60% yield and 97:3 dr [(*Z*):(*E*) ratio].¹¹ An analogous sequence of reactions applied to 8 initially gave secondary amine 13 in 59% yield and 97:3 dr [(*Z*):(*E*) ratio],¹¹ with hydrolysis giving (*2R*,*3R*,*Z*)-14 in 62%

yield and 97:3 dr [(Z):(E) ratio].¹¹ Given the known enantiomeric purity of the (*R*)-*tert*-butylsulfonamide **4** (i.e., >98% ee) employed for the formation of imine **5**, the enantiomeric purities of **5**, **7–9**, and **11–14** can be confidently inferred as >98% ee (Scheme 3).

Scheme 3



Comparison of the ¹H and ¹³C NMR data reported for natural nakinadine A by Kobayashi et al.^{1,19} with those of our authentic samples of (2*S*,3*R*,*Z*)-**12** and (2*R*,3*R*,*Z*)-**14** (Figure 3) revealed good agreement of the chemical shifts reported for the natural product with those of **12** in particular in the key regions of the spectra containing the resonances associated with the β-amino acid moiety [C(21)H, C(22)H, C(21), C(22), and C(24)], thus supporting the relative configuration assignment of Kobayashi et al.¹ For the natural product, Kobayashi et al. reported the specific rotation [α]_D²³ −3 (c 1.0 in CHCl₃),¹ while our sample of (2*S*,3*R*,*Z*)-**12** has a specific rotation of [α]_D²⁰ −15.7 (c 1.0 in CHCl₃). Although the magnitudes of these specific rotation values do not match closely, their

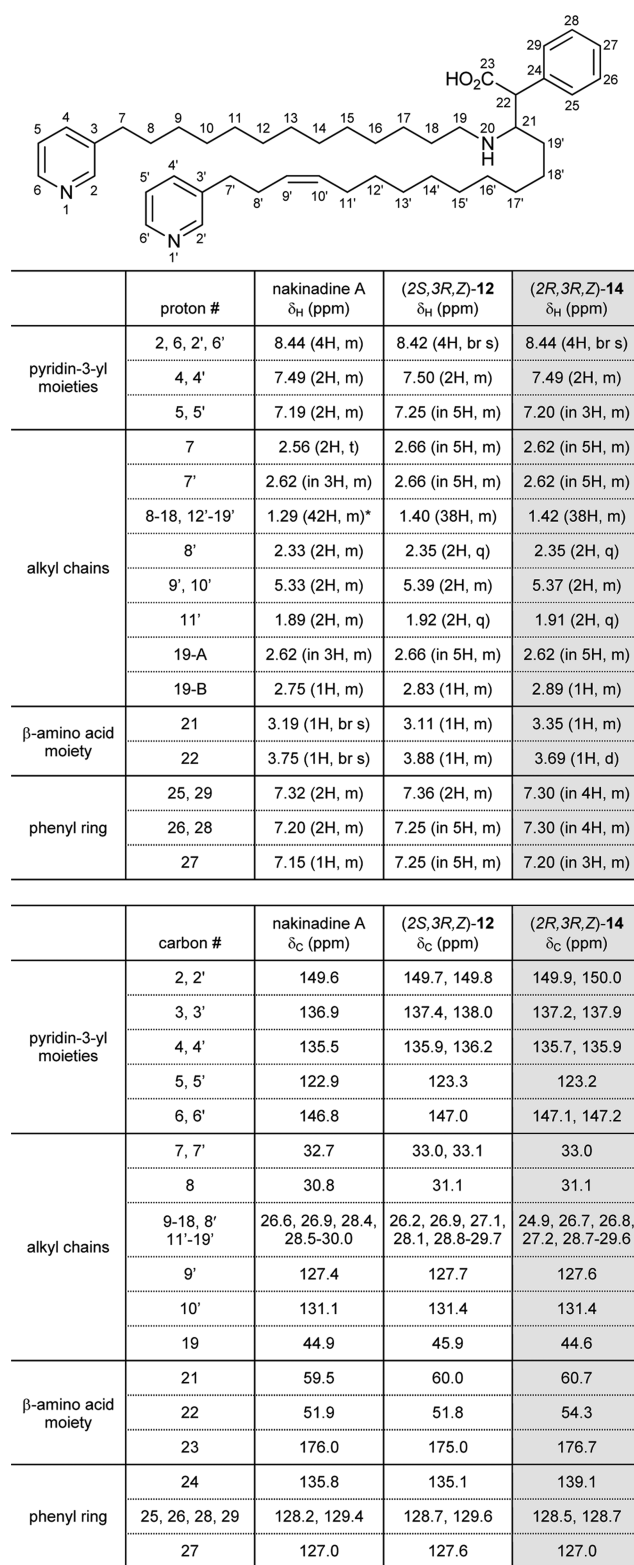


Figure 3. ¹H and ¹³C NMR spectroscopic data for “natural” (–)-nakinadine A, “synthetic” (2*S*,3*R*,*Z*)-**12**, and “synthetic” (2*R*,3*R*,*Z*)-**14**. The numbering convention adopted by Kobayashi et al. (ref 1) has also been adopted here. *The (unassigned) ¹H NMR data for the natural product (C₄₅H₆₇N₃O₂) includes 69 protons in total. Resonances corresponding to the protons of the long alkyl chains are reported at 1.0–1.4 (34H, m), 1.42 (2H, m), 1.43 (2H, m), 1.54 (2H, m), 1.57 (2H, m); the midpoint of these has been quoted here for purposes of comparison.

identical signs suggest that natural (–)-nakinadine A is the (2*S*,3*R*,*Z*)-stereoisomer **12**. The absolute (2*S*)-configuration is also in accordance with the absolute (2*S*)-configurations assigned by Kobayashi et al.² to nakinadines B and C. On this basis, it seems likely that this family of alkaloids are homochiral at C(2); in turn, considering the relative (*RS*,*SR*)-configurations assigned to nakinadines D–F by Kobayashi et al.,² it is thus proposed that these family members also share the absolute (2*S*,3*R*)-configuration.

In conclusion, the first asymmetric syntheses of both possible diastereoisomers (excluding geometric isomers) of the reported structure of the marine alkaloid nakinadine A has been achieved. These syntheses rely on the asymmetric Mannich-type reaction of methyl phenylacetate with the sulfinamide derived from (*R*)-*tert*-butylsulfinamide and (*Z*)-14-(pyridin-3'-yl)tetradec-11-enal as the key stereodefining step. The synthesis of the (2*S*,3*R*,*Z*)-stereoisomer proceeded in 10 steps and 10% overall yield, while the synthesis of the (2*R*,3*R*,*Z*)-stereoisomer proceeded in 11 steps and 9% overall yield. Comparison of ¹H and ¹³C NMR spectroscopic and specific rotation data for these synthetic samples with those reported for the natural product allowed assignment of the absolute (2*S*,3*R*,*Z*)-configuration within natural (–)-nakinadine A. Further application of this methodology to facilitate the asymmetric synthesis of the remaining members of the nakinadine alkaloid family is currently under investigation within our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of ¹H and ¹³C NMR spectra, and crystallographic information file (for structure CCDC 977827). 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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- (11) The (*Z*):(*E*) ratio was assigned from integration of the resonances associated with the allylic protons [C(10)*H*₂ or C(10')*H*₂] in the 700 MHz ¹H NMR spectrum.
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- (13) In the case of the lithium enolates (generated from treatment with LiHMDS), the (*E*):(*Z*) ratio was determined by trapping with TMSCl at –78 °C to give a mixture of the corresponding silyl enol ethers, which was analyzed by ¹H NMR spectroscopy. In the case of the magnesium enolates (generated from treatment with MeMgBr), several attempts at this trapping procedure consistently returned only starting material.
- (14) A more accurate ratio of (2*S*,3*R*,*R_S*,*Z*)-**7**:(2*R*,3*R*,*R_S*,*Z*)-**8** could not be determined from the ¹H NMR spectrum of the crude reaction mixture due to peak overlap, the presence of the corresponding (2*S*,3*R*,*R_S*,*E*)- and (2*R*,3*R*,*R_S*,*E*)-diastereoisomers, and other minor impurities.
- (15) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 977827. See the Supporting Information for further details.
- (16) Analysis of the crystal used for the X-ray structure determination by ¹H NMR spectroscopy (on a 500 MHz instrument fitted with a 1 mm microprobe) confirmed that it was representative of the bulk sample.
- (17) A sample of **7** was also isolated from this reaction, in 10% yield and 97:3 dr [(*Z*):(*E*) ratio].
- (18) Attempted use of a higher temperature (and hence shorter reaction time) to effect the ester hydrolysis led to competing hydration of the olefin.
- (19) Unfortunately, Professor Kobayashi was unable to provide either an authentic sample of the natural product or copies of the original characterization data for comparison.