JOC Article

Synthesis of Naturally Occurring Pyridine Alkaloids via Palladium-Catalyzed Coupling/Migration Chemistry

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The palladium-catalyzed cross-coupling of 3-iodopyridine, long-chain terminal dienes, and benzylic amines or tosylamides provides a novel route to key intermediates for the synthesis of the naturally occurring, biologically active pyridine alkaloids theonelladins C and D, niphatesine C, and xestamine D. This process involves (1) oxidative addition of the heterocyclic iodide to Pd(0), (2) carbopalladation of the least hindered carbon−carbon double bond of the diene, (3) palladium migration, and (4) π-allylpalladium displacement by the nitrogen nucleophile with simultaneous regeneration of the Pd catalyst. Subsequent hydrogenation and deprotection affords good yields of the natural products. The Pd-catalyzed coupling of 3-iodopyridine and 2-methyl-11-dodecen-1-ol provides a convenient synthesis of a long-chain aldehyde by an analogous palladium migration process, which is easily converted to the pyridine alkaloid ikimine A.

Introduction

Recently, many pyridine alkaloids have been isolated from marine organisms and shown to exhibit interesting biological activity. For example, the antileukemic and antineoplastic theonelladins C (**1**) and D (**2**) have been isolated from the Okinawan marine sponge *Theonella swinhoei*.[1] The antileukemic niphatesines C (**3**) and D (**4**) and the cytotoxic and antimicrobial niphatesine G (**5**) have been obtained from the Okinawan marine sponge *Niphates* sp.[1c,2] The cytotoxic ikimines A−C (**6**−**8**, respectively) have been isolated from a Micronesian sponge.[2b,3] The antimicrobial xestamine C (**9**) comes from a Caribbean sponge *Xestospongia wiedenmayeri*, while the antimicrobial xestamines D−H (**10**−**13**, respectively) have been extracted from a Bahamian sponge *Calyx podatypa*.[4] 3-Pyridine alkaloids such as the navenones,[5] halitoxins,[6] niphatynes,[7] niphatoxins,[8] haminols,[9] hachijodines,[10] and cribochalines[11] have also been isolated by several groups. More recently, nitro-[12] and azomethine *N*-oxide[13] variants of these pyridine alkaloids have been discovered. Some of the alkaloids containing a 3-pyridyl group on one end of a saturated chain and simple amine functionality on the other have been synthesized. Rao et al. reported the first total synthesis of theonelladins A−D using a Wittig reaction for construction of the carbon skeleton.[1b] Six steps were required to complete the total synthesis of theonelladins C and D. Sulfone alkylation chemistry has also been utilized to prepare theonelladin D.[1d] Grignard or alkyne alkylation chemistry have also been employed to synthesize theonelladins A−D, as well as niphatesine A[1c] and hachijodines F and G.[10b] Niphatesines A−D have been prepared by Friedel−Crafts acylation, Wittig, Heck, and alkyne alkylation chemistry.[2c−e] The only prior synthesis of ikimine A also employed a Friedel−Crafts acylation.[3b] There presently exist no syntheses of any of the xestamines. To date, no general synthetic strategy applicable to any chain length has been employed to prepare a variety of these interesting alkaloids in a minimum of steps.

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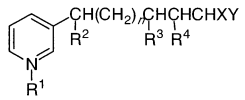
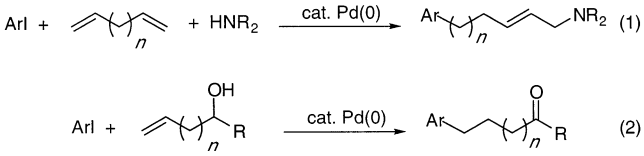


	R^1	R^2	R^3	R^4	*n*	X, Y
Theonelladin C (**1**)	-	H	H	H	9	H, NH_2
Theonelladin D (**2**)	-	H	H	H	9	H, NHMe
Niphatesine C (**3**)	-	H	H	Me	8	H, NH_2
Niphatesine D (**4**)	-	H	Me	H	8	H, NH_2
Niphatesine G (**5**)	-	H	H	Me	9	=NOMe
Ikimine A (**6**)	-	H	H	Me	8	=NOMe
Ikimine B (**7**)	-	H	Me	H	8	=NOMe
Ikimine C (**8**)	-	H	H	H	9	H, NHOMe
Xestamine C (**9**)	-	Me	H	H	10	H, NMe(OMe)
Xestamine D (**10**)	-	H	H	H	10	H, NMe(OMe)
Xestamine E (**11**)	-	H	H	H	11	H, NMe(OMe)
Xestamine G (**12**)	Me^+	H	H	H	10	H, NMe(OMe)
Xestamine H (**13**)	Me^+	H	H	H	11	H, NMe(OMe)

FIGURE 1. Some naturally occurring pyridine alkaloids.

We have recently reported several palladium-catalyzed migration processes, which are extraordinarily efficient for the construction of long-chain compounds with an aromatic ring on one end of the chain and some kind of functionality on the other end of the chain. For example, the palladium-catalyzed cross-coupling of aryl halides, 1,ω-dienes, and carbanions[14] or amines[15] provides a highly efficient route to long-chain carbonyl or amine products (eq 1). In an analogous fashion, the palladium-catalyzed cross-coupling of aryl halides and ω-alken-1-ols provides long-chain carbonyl products quite efficiently (eq 2).[16]

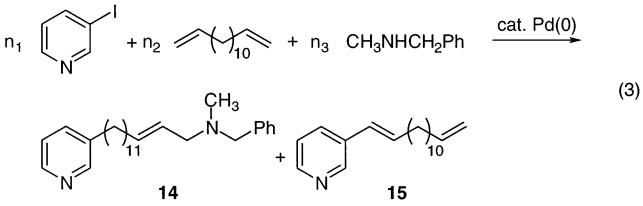


The beauty of this methodology is that one can readily employ a wide range of aromatic substrates, dienes and alkenols of varying chain length, and various nucleophiles to prepare a tremendous range of products in one easy step. This chemistry appeared to be ideal for the synthesis of the pyridine alkaloids discussed above. Indeed, we now report very efficient syntheses of theonelladins C and D, niphatesine C, xestamine D, and ikimine A using this methodology.[17]

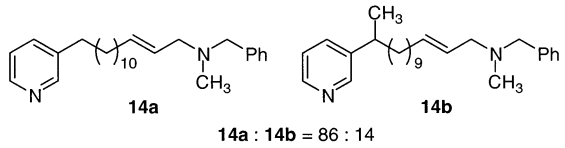
Results and Discussion

Total Synthesis of Theonelladins C and D. To prepare theonelladins C and D using the methodology outlined in eq 1, we required three major components: 3-iodopyridine, 1,12-tridecadiene, and an appropriate nitrogen nucleophile. The choice of nitrogen nucleophile turns out to be critical to the success of this approach. Unfortunately, ammonia and primary amines do not usually work well in this three-component coupling process. However, secondary amines generally afford high yields of the desired long-chain amines.[15] Since the benzyl group ($PhCH_2$) is often used as a protecting group for amines and is easily removed by a variety of methods,[18] benzylmethylamine and dibenzylamine were chosen as the most appropriate nucleophiles for synthesis of the theonelladins.

In our exploratory studies, 1,13-tetradecadiene was used as a model for 1,12-tridecadiene, since it is commercially available and 1,12-tridecadiene is not. Based on our previous work, the coupling of 3-iodopyridine, 1,13-tetradecadiene and benzylmethylamine was examined (eq 3).



We have examined the effect on the yield and ratio of **14** and **15** of the solvent (DMSO and DMF), the stoichiometry of the reactants in eq 3 (n_1, n_2, and n_3), and the number of equivalents of added LiCl. The best result was obtained when the reaction was run in DMF in the presence of 1 equiv of LiCl at 100 °C for 24 h with a 1:2.5:2 ratio of 3-iodopyridine, diene, and amine. The isolated product **14** was examined by GC-MS and ^{1}H NMR spectroscopy and found to be a mixture of two isomers in a ratio of 86:14.



The minor isomer (**14b**) is formed by addition of the pyridylpalladium intermediate to the more hindered internal carbon of one of the double bonds of the diene. Unfortunately, these two isomers are not easily separated.

It appeared that a carbon analogue of theonelladin D bearing one more methylene unit could be easily obtained simply by hydrogenation of the double bond and debenzylation of compound **14a**. The traditional procedure for debenzylation of benzylamines is heterogeneous catalytic hydrogenation.[19] It was hoped that compound **14a** would undergo hydrogenation of the double bond and debenzylation simultaneously.

Pearlman's catalyst,[20] 20% $Pd(OH)_2$ on charcoal, has proven to be an effective catalyst for debenzylation, even when other palladium catalysts have failed.[21] Thus, the

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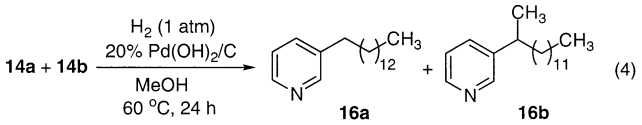
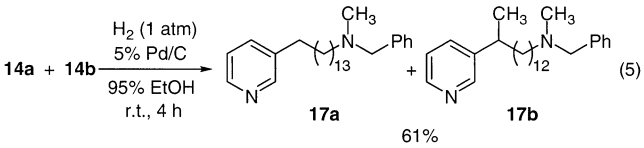
mixture of compounds **14a** and **14b** was hydrogenated using Pearlman's catalyst (eq 4).



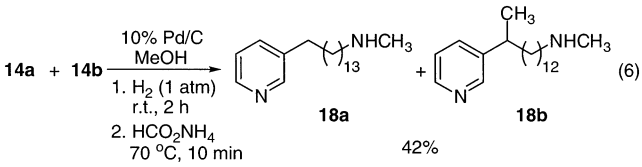
(4)

Unfortunately, none of the desired theonelladin D analogue was formed. 3-*n*-Tetradecylpyridine (**16a**) and the branched isomer **16b** were isolated along with an unknown product, which proved to be a major component. Apparently, compounds **16a** and **16b** were formed by cleavage of the allylic C−N bond. Allylic amines, like benzylic amines, can be cleaved at the C−N bond by catalytic hydrogenation.[22] We, therefore, decided to saturate the carbon−carbon double bond first and then remove the benzyl group. Hydrogenation of the C−C double bond in the mixture of compounds **14a** and **14b** proceeded smoothly under mild conditions as shown in eq 5.



(5)

Debenzylation is usually carried out by high-pressure catalytic hydrogenation.[19b,c,23] This was not particularly attractive to us. Ram et al.[24] have reported a more convenient debenzylation procedure using ammonium formate as a hydrogen source and 10% Pd/C as a catalyst. We have successfully applied Ram's procedure to the conversion of compound **17a** to the theonelladin D analogue **18a**. To simplify the procedure, the same catalyst and solvent were used for sequential hydrogenation of the carbon−carbon double bond and debenzylation without purification or separation of the intermediates. Thus, a mixture of compounds **14a** and **14b** was dissolved in methanol and flushed with 1 atm of H_2 gas in the presence of 10% Pd/C at room temperature for 2 h. Then, 6 equiv of HCO_2NH_4 was added to the reaction mixture. The mixture was stirred at 70 °C for 10 min, and the products **18a** and **18b** were obtained in 42% combined yield (eq 6).

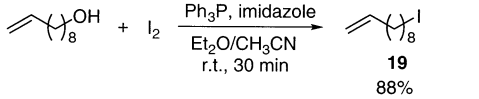


(6)

To obtain better yields of the products, several different palladium catalysts were examined in this reaction. Using 5% (0.10 equiv of Pd) or 10% Pd/C (0.35 equiv of Pd) gave isolated yields of a mixture of **18a** and **18b** of 54 and 42%, respectively. On the other hand, 0.20, 0.35, or 0.75 equiv of Pd as 20% $Pd(OH)_2/C$ gave 46, 76, and 75% yields, respectively. Thus, Pearlman's catalyst gave the best results, provided approximately 0.35 equiv of the Pd catalyst was employed.

We have tried to simplify this procedure still further. For example, a mixture of compounds **14a** and **14b** was mixed with HCO_2NH_4 and 20% $Pd(OH)_2/C$ in methanol and flushed with 1 atm of H_2 at room temperature. This approach afforded the anticipated mixture of **18a** plus **18b** in 53% yield. Alternatively, a mixture of **14a** and **14b** plus HCO_2NH_4 and 20% $Pd(OH)_2/C$ in methanol was simply refluxed without flushing with H_2. This provided a 43% yield of a mixture of **18a** plus **18b**. Thus, unfortunately, neither effort provided better results.

With proven procedures for the palladium-catalyzed coupling, hydrogenation, and debenzylation in hand, we were ready to synthesize the natural product theonelladin D by substituting 1,12-tridecadiene for 1,13-tetradecadiene. Although the former diene is not commercially available, it is easily made from 9-decen-1-ol in two steps. Thus, 9-decen-1-ol was allowed to react with iodine in the presence of PPh_3 and imidazole[25] to give 10-iodo-1-decene (**19**) in 88% yield (eq 7). The copper-catalyzed coupling of 10-iodo-1-decene with allylmagnesium bromide[26] afforded a 60% yield of 1,12-tridecadiene (**20**) (eq 8).



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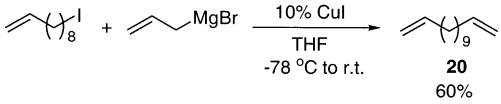
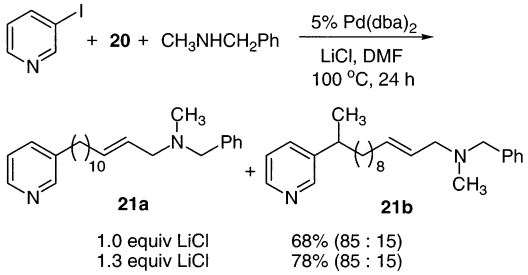


(8)

1,12-Tridecadiene was then employed in the palladium-catalyzed coupling reaction under our "optimal" reaction conditions. The desired coupling products (**21a** and **21b**) were isolated in a 68% combined yield in a ratio of 85:15 (eq 9). We have found that slightly increasing the amount of LiCl afforded a still better 78% yield.



(9)

Finally, the hydrogenation and debenzylation of compounds **21a** and **21b** afforded the natural product theonelladin D (**2**) and its isomer (**22**) in a 70% combined yield (eq 10).

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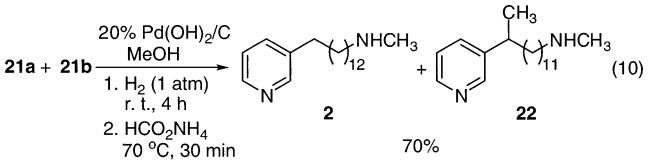
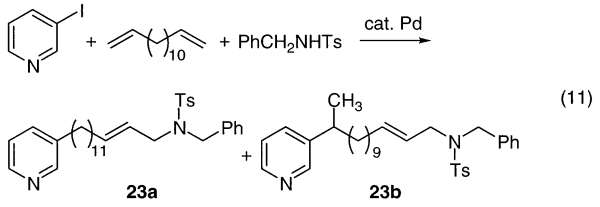


Theonelladin C having an NH_2 group at the end of the carbon chain was our next synthetic target. As in the synthesis of theonelladin D, the key issue here is the choice of the nitrogen nucleophile for use in the palladium reaction. On the basis of the success of our debenzylation process, benzylamine and dibenzylamine were chosen as nucleophiles. In our exploratory work with these nucleophiles, commercially available 1,13-tetradecadiene was again used as a substitute for 1,12-tridecadiene.

When employed in the palladium-catalyzed coupling, benzylamine failed to give the desired product. Our previous work indicated that 1° amines were generally not as good as 2° amines as nucleophiles.[15] We, therefore, anticipated that dibenzylamine would provide better results. Surprisingly, dibenzylamine did not work well in this coupling process either. We tried to improve this reaction by changing the chloride reagent added, adding a base, extending the reaction time and using a short-chain diene. Unfortunately, the reactions employing 1,13-tetradecadiene gave very low yields of the desired coupling product and even 1,5-hexadiene gave yields no higher than approximately 35%, and the products were rather impure.

It appeared that another protecting group was necessary. The protecting group had to facilitate the palladium process itself and be easily removed after the palladium reaction. The tosyl group is well-known as a useful protecting group for amines,[18] and tosylamides are generally good nucleophiles in π-allylpalladium coupling processes.[27] *N*-Benzyl tosylamide was therefore examined in our palladium-catalyzed three-component coupling. The results from the coupling of 3-iodopyridine, 1,13-tetradecadiene, and *N*-benzyl tosylamide are summarized in eq 11 and Table 1.



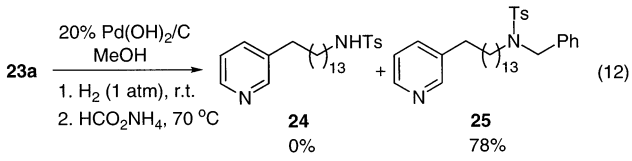
From Table 1, one can see that *N*-benzyl tosylamide is a relatively good nucleophile in this coupling reaction once appropriate reaction conditions have been determined. The results indicate that an excess of base is required to get a good yield and Na_2CO_3 is better than $NaHCO_3$. The use of LiCl slowed the reaction considerably. No improvement was observed by either adding PPh_3 or lowering the temperature.

TABLE 1. Palladium-Catalyzed Coupling of 3-Iodopyridine, 1,13-Tetradecadiene, and *N*-Benzyl Tosylamide (eq 11)[a]

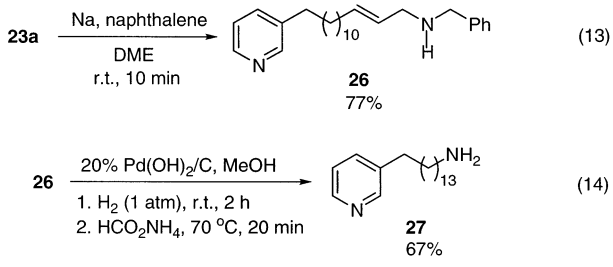
entry	*n*-Bu_4NCl (equiv)	Na_2CO_3 (equiv)	temp (°C)	time (h)	% isolated yield **23a**	% isolated yield **23b**
1	1	4	100	24	50[b]	
2	*c*	0	100	24	*d*	
3	1	2	100	48	46[b]	
4	1	*e*	100	48	23	5
5[f]	1	4	100	48	37	7
6	1	4	80	48	23	5
7	2	4	100	24	58	11

[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$ in DMF using 2.5 equiv of 1,13-tetradecadiene and 2 equiv of *N*-benzyl tosylamide. [b] Combined yield of **23a** and **23b**. [c] Used 1 equiv of LiCl. [d] Reaction was very slow, and the yield was not determined. [e] Used 4 equiv of $NaHCO_3$. [f] Ph_3P (5 mol %) was added.

There is an additional benefit to be gained by using the tosylamide protecting group. Unlike the products of the palladium reactions of benzylmethylamine, the coupling products **23a** and **23b** could be readily separated by flash chromatography. This permits the synthesis of pure theonelladin C as a single isomer after deprotection and hydrogenation. We first tried to apply our earlier procedure for hydrogenation and debenzylation to compound **23a**. Unfortunately, debenzylation did not occur and only the hydrogenation product **25** was formed in 78% yield (eq 12). This suggests that this debenzylation procedure is only effective on *N*-benzylamines, not on *N*-benzyl tosylamides. Therefore, the tosyl group must be removed first.

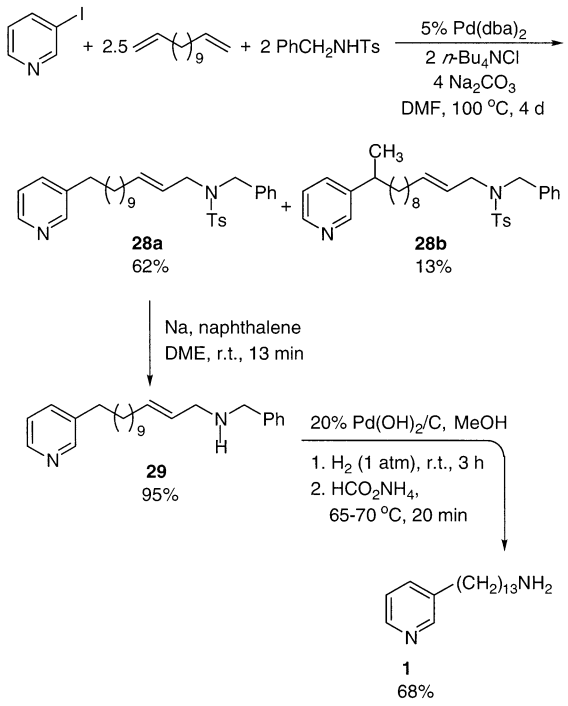


Ji et al. have reported a very efficient method for the cleavage of sulfonamides.[28] The N−S bond in sulfonamides is cleaved by the anion radical formed from Na and naphthalene under very mild conditions. We applied their procedure to our tosylamide coupling product. Compound **23a** was treated with 8 equiv of sodium naphthalenide in dimethoxyethane at room temperature for 10 min to give the detosylation product **26** in 77% yield (eq 13). Compound **26**, a benzylamine, was then hydrogenated and debenzylated as before to give the theonelladin C analogue **27** in 67% yield (eq 14).



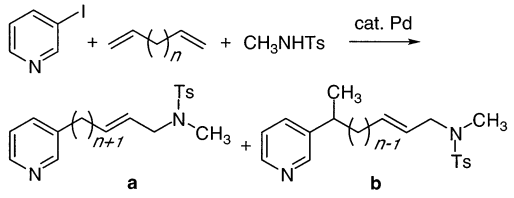
(27) (a) Larock, R. C.; Berríos-Peña, N. G.; Fried, C. A.; Yum, E. K.; Tu, C. Leong, W. *J. Org. Chem*. **1993**, *58*, 4509. (b) Larock, R. C.; Yum, E. K. *Synlett* **1990**, 529. (c) Larock, R. C.; Berríos-Peña, N. G.; Fried, C. A. *J. Org. Chem*. **1990**, *55*, 2615. (d) Larock, R. C.; Berríos-Peña, N. G.; Narayanan, K. *J. Org. Chem*. **1990**, *55*, 3447. (e) Inoue, Y.; Taguchi, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn*. **1985**, *58*, 2721. (f) Byström, S. E.; Aslanian, R.; Bäckvall, J.-E. *Tetrahedron Lett*. **1985**, *26*, 1749. (g) Stolle, A.; Ollivier, J.; Piras, P. P.; Salaün, J.; de Meijere, A. *J. Am. Chem. Soc*. **1992**, *114*, 4051. (h) Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem*. **1993**, *58*, 6826.

SCHEME 1



With successful procedures in hand for the preparation of the theonelladin analogue **27**, synthesis of the natural product theonelladin C (**1**) was tackled using 1,12-tridecadiene instead of 1,13-tetradecadiene in the palladium-catalyzed cross-coupling, followed by deprotection and hydrogenation (Scheme 1). The coupling of 3-iodopyridine, 1,12-tridecadiene, and *N*-benzyl tosylamide afforded the desired product **28a** and its isomer **28b** in 62 and 13% yields, respectively. Compound **28a** was converted into benzylamine **29** in 95% yield upon treatment with sodium naphthalenide. Finally, theonelladin C was obtained in 68% yield from the hydrogenation and debenzylation of **29**.

The successful synthesis of theonelladin C using a tosylamide as a nucleophile in the palladium-catalyzed cross-coupling encouraged us to attempt the synthesis of theonelladin D by a similar process. Commercially available *N*-methyl tosylamide was therefore chosen as the nucleophile for the coupling reaction. It was anticipated that *N*-methyl tosylamide would be a good nucleophile and the desired coupling product should be easily separated from its isomer.



(15)

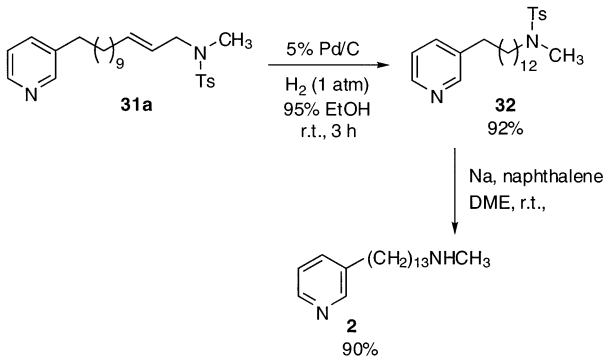
Some results from the palladium-catalyzed coupling of 3-iodopyridine, 1,12-tridecadiene or 1,13-tetradecadiene, and *N*-methyl tosylamide are summarized in eq 15 and Table 2. First, 1,13-tetradecadiene was again used as a substitute for 1,12-tridecadiene (entries 1 and 2). Compared with *N*-benzyl tosylamide (Table 1), *N*-methyl tosylamide underwent a slower coupling reaction, and 4 days were required to get good results. The desired product **31a** was obtained in 59% isolated yield as a single isomer from the coupling of 3-iodopyridine, 1,12-tridecadiene, and *N*-methyl tosylamide (entry 4).

TABLE 2. Palladium-Catalyzed Coupling of 3-Iodopyridine, Nonconjugated Dienes, and *N*-Methyl Tosylamide (eq 15)[a]

entry	*n*	base (equiv)	time (d)	product, % yield	
1	10	Na_2CO_3 (4)	1	**30a**, 28	**30b**, [b]
2	10	Na_2CO_3 (4)	2	**30a**, 42	**30b**, [b]
3[c]	9	Na_2CO_3 (4)	4	**31a**, 50	**31b**, [b]
4[d]	9	Na_2CO_3 (4)	4	**31a**, 59	**31b**, 11
5	9	NaH (2)	4	**31a**, 40	**31b**, 8

[a] Reactions were run in DMF in the presence of 5 mol % $Pd(dba)_2$ and 2 equiv of *n*-Bu_4NCl using 2.5 equiv of diene and 2.0 equiv of *N*-methyl tosylamide at 100 °C. [b] Not determined. [c] Crude products treated with NaH to remove excess CH_3NHTs. [d] Crude products treated with NaOH to remove excess CH_3NHTs.

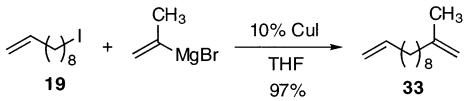
SCHEME 2



Theonelladin D was finally obtained through the hydrogenation and subsequent detosylation of compound **31a**. As shown in Scheme 2, the C−C double bond of compound **31a** was saturated by H_2 using 5% Pd/C as a catalyst to give a 92% yield of compound **32**, which, in turn, was treated with fresh radical anion formed from Na and naphthalene to afford theonelladin D in 90% yield.

Total Synthesis of Niphatesine C. Niphatesine C has a structure very similar to theonelladin C. They both have amino and 3-pyridyl groups at the ends of a long carbon chain. Niphatesine C contains a saturated 12-carbon chain with a methyl group on the second carbon from the amine, while theonelladin C contains a straight, saturated 13-carbon chain. Therefore, all of the procedures used to prepare theonelladin C should be applicable to the synthesis of niphatesine C. One should only need to replace the 1,12-tridecadiene with 2-methyl-1,11-dodecadiene (**33**).

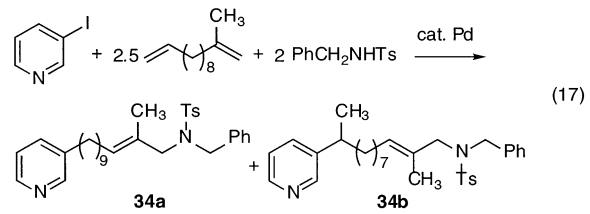
Diene **33** was easily prepared in an excellent yield by the copper-catalyzed reaction of 10-iodo-1-decene and isopropenylmagnesium bromide (eq 16).



(16)

(28) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311.

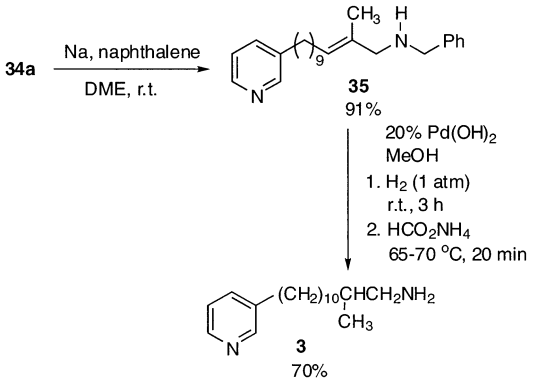
Diene **33** was then employed in the palladium-catalyzed coupling with 3-iodopyridine and *N*-benzyl tosylamide (eq 17). The reaction was very slow, and only after 5 days was a satisfactory yield of 61% of the desired tosylamide **34a** obtained, along with 13% of the isomer **34b**.



(17)

With the coupling product **34a** readily separable from **34b**, it would appear that niphatesine C could be readily prepared by detosylation, hydrogenation, and debenzylation (Scheme 3). Indeed, compound **34a** was treated

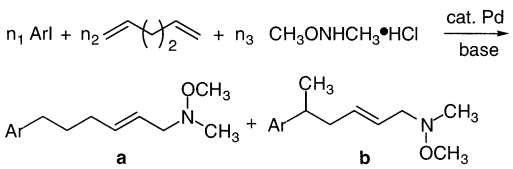
SCHEME 3



with the radical anion formed from Na and naphthalene to give the detosylated product **35** in 91% yield. Then, compound **35** underwent hydrogenation and debenzylation catalyzed by 20% $Pd(OH)_2$ in MeOH to afford the natural product niphatesine C (**3**) in 70% yield.

Total Synthesis of Xestamine D. The interesting alkaloid xestamine D (**10**) contains a 14-carbon chain with a simple 3-pyridyl group on one end and an *N*-(methoxyl)methylamine on the other end. It appeared that this natural product might be easily synthesized using our palladium chemistry and *N*,*O*-dimethylhydroxylamine, 1,13-tetradecadiene, and 3-iodopyridine, all of which are readily available. The critical question is whether *N*,*O*-dimethylhydroxylamine will successfully undergo the palladium coupling.

In our initial investigation of this question, a short-chain diene was used in order to simplify the reaction. In addition to 3-iodopyridine, iodobenzene was also examined. The results are summarized in eq 18 and Table 3.



(18)

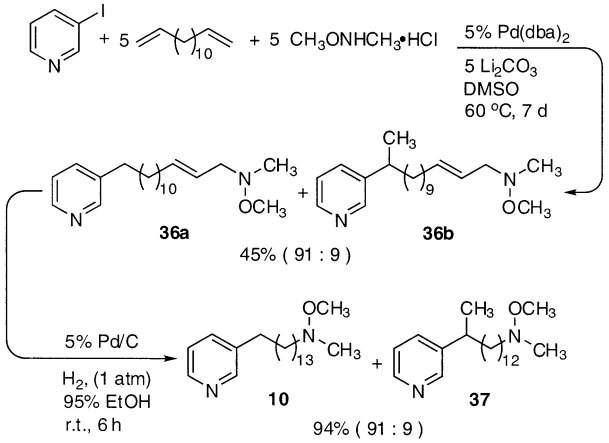
Since *N*,*O*-dimethylhydroxylamine is only commercially available as the hydrochloride salt, another base

TABLE 3. Palladium-Catalyzed Coupling of Aryl Iodides, 1,5-Hexadiene, and *N*,*O*-Dimethylhydroxylamine (eq 18)[a]

entry	ArI	$n_1/n_2/n_3$	solvent	base (equiv)	temp (°C)	time (days)	% yield (ratio)
1	PhI	1/5/2	DMF	Na_2CO_3 (2)	100	2	trace
2		1/5/5	DMSO	Na_2CO_3 (5)	100	1	14[b]
3		1/5/5	DMSO	Na_2CO_3 (5)	60	2	39[b]
4		1/5/5	DMSO	Na_2CO_3 (5)	rt	4	<20[b]
5		1/5/5	DMF	Na_2CO_3 (5)	60	2	trace
6		1/5/5	DMA	Na_2CO_3 (5)	60	2	trace
7	PyI[c]	1/5/5	DMSO	Na_2CO_3 (5)	60	2	46 (95:5)
8		1/5/2	DMSO	Na_2CO_3 (2)	60	2	45[b]
9[d]		1/5/5	DMSO	Li_2CO_3 (5)	60	1	43 (97:3)

[a] Reactions were run in the presence of 5 mol % $Pd(dba)_2$ and 2 equiv of *n*-Bu_4NCl. [b] Ratios were not determined. [c] 3-Iodopyridine. [d] *n*-Bu_4NCl was not added.

SCHEME 4



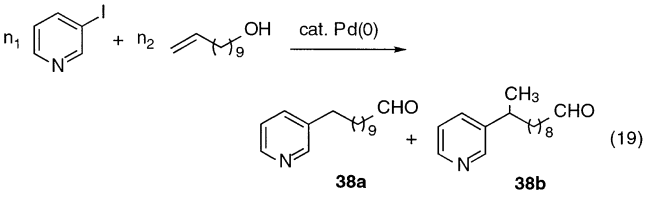
is needed in the reaction system to release the hydroxylamine. From Table 3, one can see that DMSO is a suitable solvent for this coupling reaction, and the temperature is crucial. The reaction was very slow at room temperature (entry 4), but a temperature of 100 °C also gave only a very low yield of the desired product (entry 2). The same reaction run at 60 °C, however, gave a better yield, although it was still not very satisfactory (entry 3). Fortunately, 3-iodopyridine gave somewhat better results than iodobenzene in this coupling process and generally afforded a modest yield of the desired product (entries 7−9). It was observed that Na_2CO_3 did not completely dissolve in the solvent (DMSO) during the reaction. Li_2CO_3 was therefore used, because (1) it is more soluble in most organic solvents and (2) neutralizing HCl would generate LiCl, which might substitute for *n*-Bu_4NCl, which has proven to be useful in many of these coupling reactions. The reaction run with Li_2CO_3 (entry 9) was faster than that of Na_2CO_3 and gave about the same yield. Remarkably, the use of *N*,*O*-dimethylhydroxylamine provided much better regioselectivity than alkylamines or tosylamides in the arylpalladation step of the coupling process.

The reaction conditions described in entry 9 of Table 3 were then applied to the coupling of 3-iodopyridine, 1,13-tetradecadiene, and *N*,*O*-dimethylhydroxylamine, and the desired product **36a** was obtained in 45% yield, along with a small amount of an isomer **36b** (Scheme 4). Interestingly, the reaction with the long chain diene was

much slower than that of 1,5-hexadiene. The efficient catalytic hydrogenation of **36a** afforded xestamine D in 94% yield.

Synthesis of Ikimine A. Our previous work on the synthesis of long-chain aromatic aldehydes and ketones by the palladium-catalyzed cross-coupling of aryl halides and ω-alken-1-ols (eq 2)[16] suggested a very efficient route to ikimine A by the reaction of 3-iodopyridine and 2-methyl-11-dodecen-1-ol and subsequent oxime formation.

The reaction of 3-iodopyridine and 10-undecen-1-ol was chosen as a model system to optimize the palladium-catalyzed cross-coupling procedure, since this alcohol is commercially available (eq 19).

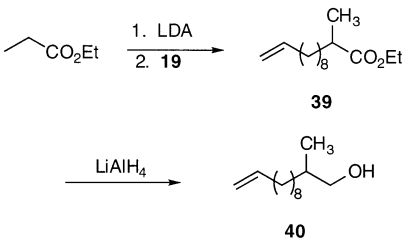


(19)

After studying the effect on the yield of **38a** and **38b** of the stoichiometry (n_1 and n_2), the percent of palladium catalyst, and the temperature and the reaction time, we found that the optimal procedure for the coupling reaction utilizes 0.5 mmol of 3-iodopyridine, 1.0 mmol of 10-undecen-1-ol, 5 mol % $Pd(OAc)_2$, 2 equiv of *n*-Bu_4NCl, 2.5 equiv of LiOAc, and 1 equiv of LiCl at 65 °C in 1 mL of DMF. An 86:14 mixture of the desired product **38a** and its regioisomer **38b** was obtained in 80% combined yield. With this method in hand, we reasoned that we should be able to easily synthesize ikimine A by simply changing the alcohol from 10-undecen-1-ol to 2-methyl-11-dodecen-1-ol.

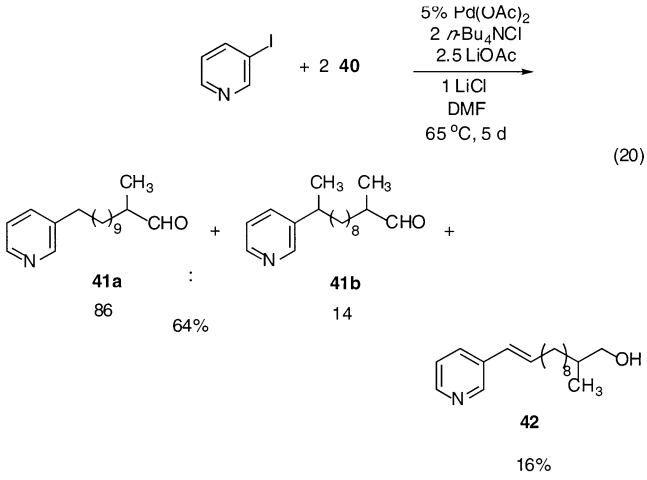
The required starting material 2-methyl-11-dodecen-1-ol was easily synthesized in two simple steps. The ester enolate of ethyl propionate was alkylated by 10-iodo-1-decene (**19**) prepared previously in 88% yield (eq 7) to form ethyl 2-methyl-11-dodecenoate (**39**), which was subsequently reduced by $LiAlH_4$ to afford an 86% yield of 2-methyl-11-dodecen-1-ol (**40**) (Scheme 5).

SCHEME 5

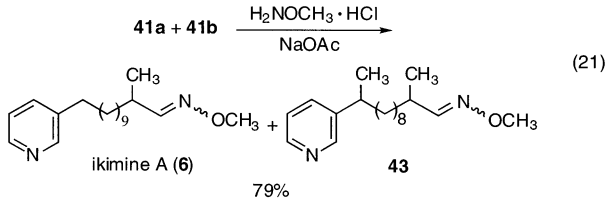


The "optimal" palladium coupling procedure was next employed to give a mixture of compounds **41a** and **41b** in a 64% combined yield (eq 20). The yield is somewhat lower than that of the model reaction, and a 16% yield of the Heck product 2-methyl-12-(3-pyridyl)-11-dodecen-1-ol (**42**) was also isolated from the reaction.

The mixture of **41a** and **41b** was subsequently reacted with methoxylamine to provide ikimine A (**6**) and its regioisomer **43** (eq 21). Ikimine A was isolated by preparative TLC. This compound consists of both anti and syn isomers in a ratio of 66:34. Thus, ikimine A has been synthesized in five steps from readily available starting materials and in 19% overall yield.



(20)



(21)

Conclusion

The palladium-catalyzed coupling of 3-iodopyridine, long-chain nonconjugated dienes and appropriate nitrogen nucleophiles has been successfully applied to the synthesis of the naturally occurring alkaloids theonelladins C and D, niphatesine C, and xestamine D. Only two to three steps were needed to accomplish the total synthesis of these natural products from readily available starting materials. Benzyl and tosyl groups were chosen as suitable protecting groups for the nitrogen nucleophiles, because they afforded good yields of coupling products and could be easily removed by convenient procedures.

The palladium-catalyzed coupling of 3-iodopyridine and 2-methyl-11-dodecen-1-ol has been successfully applied to the synthesis of the naturally occurring pyridine alkaloid ikimine A in five steps and 19% overall yield.

These palladium-catalyzed coupling/migration processes provide convenient approaches to the synthesis of the pyridine alkaloids and other natural products containing a long chain with an aromatic or heteroaryl group on one end of the chain and various functionality on the other end.

Experimental Section

Equipment. All proton and carbon nuclear magnetic resonance spectra were recorded at 300 and 75.5 MHz, respectively, or 400 and 100 MHz, respectively. Flash chromatography was carried out on 230−400 mesh silica gel. Thin-layer chromatography was performed using commercially prepared 60 mesh silica gel plates. Visualization was effected with short wavelength UV light (254 nm) or a basic $KMnO_4$ solution (3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of 5% NaOH + 300 mL of H_2O). Melting points are uncorrected.

Reagents. Most reagents were commercially available. 3-Iodopyridine was prepared using a literature procedure.[29]

General Procedure for the Palladium-Catalyzed Coupling of Aryl Iodides, Nonconjugated Dienes, and Amines. To a 2 dram vial with a stirring bar were added 0.25 or 0.5 mmol of aryl iodide, 0.625 or 1.25 mmol of nonconjugated diene, 0.5 or 1.0 mmol of nucleophile, 5 mol % of bis(dibenzylideneacetone)palladium, 0.5 or 1.0 mmol of *n*-Bu_4NCl (only for reactions with tosylamides), 1.0 or 2.0 mmol of Na_2CO_3 (only for reactions with tosylamides), and 1 or 2 mL of DMF, respectively, unless indicated otherwise. The vial was capped with a Teflon-lined screw-cap. The resulting mixture was stirred at 100 or 60 °C for the required period of time. The mixture was then allowed to cool to room temperature, diluted with saturated NaCl solution, and extracted with diethyl ether. The ether layer was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure to remove the solvent. The crude products were isolated by flash chromatography on a silica gel column.

Compounds 21a and 21b. Compounds **21a** and **21b** were obtained as an inseparable 85:15 mixture of isomers in 78% combined yield from the coupling of 3-iodopyridine, 2.5 equiv of 1,12-tridecadiene, and 2 equiv of benzylmethylamine in the presence of 1.3 equiv of LiCl at 100 °C for 24 h: ^{1}H NMR ($CDCl_3$) δ 1.23−1.35 (br m, 14 H), 1.60 (quintet, J = 7.2 Hz, 2 H), 2.03 (q, J = 6.0 Hz, 2 H), 2.16 (s, 3 H), 2.58 (t, J = 7.2 Hz, 2 H), 2.67 (sextet, J = 7.2 Hz, 1 H, PyCH in **21b**), 2.96 (d, J = 6.0 Hz, 2 H), 3.47 (s, 2 H), 5.51 (dt, J = 15.3, 6.0 Hz, 1 H), 5.59 (dt, J = 15.3, 6.0 Hz, 1 H), 7.18 (dd, J = 7.8, 5.1 Hz, 1 H), 7.22−7.34 (m, 5 H), 7.47 (d, J = 7.8 Hz, 1 H), 8.43 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 29.2, 29.2, 29.3, 29.4, 29.5, 29.6, 31.1, 32.4, 33.0, 37.4, 42.0, 59.7, 61.6, 123.2, 126.8, 127.0, 128.1, 129.1, 134.3, 135.7, 137.9, 139.1, 147.2, 149.9; IR (neat) 3083, 3024, 2924, 2852, 1681, 1454, 1024 cm^{-1}; HRMS for $C_{26}H_{37}N_2$ (M^+ − H) calcd 377.2957, found 377.2955.

Compound 28a. Compound **28a** was obtained in 62% yield from the coupling of 3-iodopyridine, 2.5 equiv of 1,12-tridecadiene, and 2 equiv of *N*-benzyl tosylamide using the procedure above at 100 °C for 4 days: ^{1}H NMR ($CDCl_3$) δ 1.20−1.31 (br m, 14 H), 1.61 (quintet, J = 6.9 Hz, 2 H), 1.86 (q, J = 6.0 Hz, 2 H), 2.43 (s, 3 H), 2.59 (t, J = 7.5 Hz, 2 H), 3.69 (d, J = 6.9 Hz, 2 H), 4.32 (s, 2 H), 5.07 (dt, J = 15.3, 6.9 Hz, 1 H), 5.37 (dt, J = 15.3, 6.9 Hz, 1 H), 7.19 (dd, J = 7.8, 4.8 Hz, 1 H), 7.23−7.35 (m, 5 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.73 (d, J = 8.1 Hz, 2 H), 8.43 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.6, 28.9, 29.2, 29.5, 29.6, 31.2, 32.1, 33.0, 49.0, 50.0, 123.2, 123.3, 127.2, 127.6, 128.4, 129.6, 135.8, 136.3, 136.4, 137.7, 138.0, 143.1, 147.2, 150.0 (four peaks missing due to overlap); IR (neat) 3083, 3027, 2925, 2853, 1597, 1455, 1340, 1160 cm^{-1}; HRMS for $C_{32}H_{42}N_2O_2S$ (M^+ − H) calcd 518.2967, found 518.2960.

Compound 31a. Compound **31a** was obtained in 59% yield from the coupling of 3-iodopyridine, 2.5 equiv of 1,12-tridecadiene, and 2 equiv of *N*-methyl tosylamide using the procedure above at 100 °C for 4 days: ^{1}H NMR ($CDCl_3$) δ 1.20−1.30 (br m, 14 H), 1.61 (m, 2 H), 1.97 (q, J = 6.6 Hz, 2 H), 2.42 (s, 3 H), 2.60 (t, J = 7.5 Hz, 2 H), 2.63 (s, 3 H), 3.55 (d, J = 6.6 Hz, 2 H), 5.31 (dt, J = 15.3, 6.6 Hz, 1 H), 5.56 (dt, J = 15.3, 6.6 Hz, 1 H), 7.20 (dd, J = 7.8, 4.8 Hz, 1 H), 7.31 (d, J = 8.1 Hz, 2 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.66 (d, J = 8.1 Hz, 2 H), 8.43 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 29.0, 29.1, 29.2, 29.4, 29.5, 31.1, 32.1, 33.0, 33.9, 52.4, 58.8, 123.2, 123.8, 127.4, 129.5, 134.5, 135.7, 136.2, 137.9, 143.1, 147.0, 149.8 (one peak missing due to overlap); IR (neat) 3083, 3027, 2923, 2853, 1598, 1455, 1343, 1163 cm^{-1}; HRMS for $C_{26}H_{38}N_2O_2S$ calcd 442.2654, found 442.2655.

Compound 34a. Compound **34a** was obtained in 61% yield from the coupling of 3-iodopyridine, 2.5 equiv of 2-methyl-1,11-dodecadiene, and 2 equiv of *N*-benzyl tosylamide using the procedure above at 100 °C for 5 days: ^{1}H NMR ($CDCl_3$) δ 1.15−1.32 (br m, 12 H), 1.36 (s, 3 H), 1.60 (quintet, J = 7.5 Hz, 2 H), 1.84 (m, 2 H), 2.42 (s, 3 H), 2.59 (t, J = 7.5 Hz, 2 H), 3.65 (s, 2 H), 4.26 (s, 2 H), 5.10 (t, J = 6.9 Hz, 1 H), 7.15−7.24 (m, 6 H), 7.28 (d, J = 8.1 Hz, 2 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 2 H), 8.42 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 21.5, 27.8, 29.1, 29.2, 29.3, 29.4, 29.5, 31.1, 33.0, 50.8, 56.1, 123.2, 127.2, 127.3, 128.1, 128.5, 129.5, 130.6, 135.7, 136.5, 137.4, 137.9, 143.0, 147.1, 149.9 (two peaks missing due to overlap); IR (neat) 3087, 3031, 2921, 2853, 1599, 1455, 1338, 1160 cm^{-1}; HRMS for $C_{32}H_{42}N_2O_2S$ calcd 518.2967, found 518.2960.

Compounds 36a and 36b. Compounds **36a** and **36b** were obtained as an inseparable mixture of isomers (91:9) in 45% combined yield from the coupling of 3-iodopyridine, 5 equiv of 1,13-tetradecadiene, and 5 equiv of *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of 5 equiv of Li_2CO_3 in DMSO at 60 °C for 7 days: ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 7.2 Hz, 3 H, $PyCCH_3$ in **36b**), 1.24−1.31 (br m, 16 H), 1.61 (quintet, J = 7.2 Hz, 2 H), 2.02 (q, J = 7.2 Hz, 2 H), 2.55 (s, 3 H), 2.60 (t, J = 7.2 Hz, 2 H), 3.24 (m, 2 H), 3.51 (s, 3 H), 3.52 (s, 3 H, OCH_3 in **36b**), 5.51 (dt, J = 15.3, 6.3 Hz, 1 H), 5.63 (dt, J = 15.3, 6.3 Hz, 1 H), 7.19 (dd, J = 7.8, 5.1 Hz, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 8.43 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 29.1, 29.4, 29.5, 29.6, 31.1, 32.4, 33.0, 44.5, 59.8, 62.5, 123.1, 125.1, 135.1, 135.7, 137.9, 147.1, 149.9 (four peaks missing due to overlap); IR (neat) 3083, 3026, 2924, 2853, 1574, 1460, 1361, 1049 cm^{-1}; HRMS for $C_{21}H_{36}N_2O$ calcd 332.2828, found 332.2834.

Compound 32. To 115 mg of compound **31a** in 3 mL of 95% EtOH was added 11.5 mg (10 wt %) of 5% Pd/C. The resulting mixture was stirred and flushed with H_2 (1 atm) at room temperature for 4 h. After filtration and removal of the solvent, compound **32** was obtained in 92% yield: ^{1}H NMR ($CDCl_3$) δ 1.22−1.32 (br m, 18 H), 1.50 (m, 2 H), 1.61 (m, 2 H), 2.42 (s, 3 H), 2.60 (t, J = 7.2 Hz, 2 H), 2.69 (s, 3 H), 2.96 (t, J = 7.2 Hz, 2 H), 7.19 (dd, J = 7.5, 4.2 Hz, 1 H), 7.30 (d, J = 7.8 Hz, 2 H), 7.48 (d, J = 7.5 Hz, 1 H), 7.66 (d, J = 7.8 Hz, 2 H), 8.43 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 26.5, 27.6, 29.1, 29.2, 29.4, 29.5, 31.1, 33.0, 34.5, 50.1, 59.1, 123.2, 127.3, 129.5, 134.5, 135.7, 137.9, 143.1, 147.0, 149.8 (three peaks missing due to overlap); IR (neat) 3082, 3027, 2920, 2851, 1598, 1462, 1342, 1161 cm^{-1}; HRMS for $C_{26}H_{39}N_2O_2S$ (M^+ − H) calcd 443.2732, found 443.2733.

General Procedures for the Deprotection of Tosylamides: Procedure A. To a 0.5 M solution of naphthalene in 1,2-dimethoxyethane (DME) was added 3 equiv of Na. The resulting mixture was stirred under N_2 at 25 °C for approximately 1 to 2 h. After turning dark, the mixture was stirred for an additional 2 h at this temperature. The resulting radical anion solution was added dropwise to the tosylamide in DME until a brown color lasted over 10 s. The reaction mixture was immediately poured into a saturated $NaHCO_3$ solution and extracted with methylene chloride or ether. The organic layer was dried over anhydrous Na_2SO_4; the solvent was removed and the product purified on a silica gel column. **Procedure B.** The fresh radical anion was prepared as in procedure A. The tosylamide in DME was added to this radical anion solution. The resulting mixture was stirred under N_2 at room temperature for about 10 min and then poured into a saturated NaCl solution and extracted with ether. The organic layer was dried over anhydrous Na_2SO_4; the solvent was removed and the product purified on a silica gel column.

Compound 29. Compound **29** was obtained in 95% yield from the detosylation of compound **28a** using procedure B: ^{1}H NMR ($CDCl_3$) δ 1.21−1.30 (br m, 14 H), 1.60 (m, 2 H), 2.01 (q, J = 6.6 Hz, 2 H), 2.59 (t, J = 7.5 Hz, 2 H), 3.23 (d, J = 6.0 Hz, 2 H), 3.81(s, 2 H), 3.90−4.05 (br m, 1 H), 5.52 (dt, J = 15.6, 6.0 Hz, 1 H), 5.62 (dt, J = 15.6, 6.0 Hz, 1 H), 7.19 (dd, J = 7.8, 4.8 Hz, 1 H), 7.24−7.36 (m, 5 H), 7.47 (dt, J = 7.8, 1.8 Hz, 1 H), 8.41 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 29.2, 29.3, 29.6, 29.8, 31.2, 32.4, 33.1, 51.0, 53.1, 123.2, 127.0, 127.7, 128.3, 128.4,

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133.4, 135.8, 138.0, 140.0, 147.1, 149.9 (three peaks missing due to overlap); IR (neat) 3288 (N−H), 3083, 3027, 2922, 2852, 1681, 1454, 1360, 1114 cm^{-1}; HRMS for $C_{25}H_{35}N_2(M^+ - H)$ calcd 363.2800, found 363.2797.

Compound 35. Compound **35** was obtained in 91% yield from the detosylation of compound **34a** using procedure A: ^1H NMR ($CDCl_3$) δ 1.27 (br s, 12 H), 1.60 (quintet, $J = 7.5$ Hz, 2 H), 1.65 (s, 3 H), 2.01 (m, 2 H), 2.58 (t, $J = 7.5$ Hz, 2 H), 3.16 (s, 2 H), 3.72 (s, 2 H), 5.31 (t, $J = 7.5$ Hz, 1 H), 7.18 (dd, $J = 7.5$, 4.8 Hz, 1 H), 7.22−7.32 (m, 5 H), 7.47 (d, $J = 7.5$ Hz, 1 H), 8.42 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.8, 27.8, 29.2, 29.3, 29.4, 29.5, 29.7, 31.2, 33.0, 52.8, 57.0, 123.2, 126.8, 128.2, 128.3, 132.9, 135.7, 137.9, 140.4, 147.1, 149.9 (two peaks missing due to overlap); IR (neat) 3304 (N−H), 3084, 3027, 2921, 2852, 1682, 1454, 1359, 1106 cm^{-1}; HRMS for $C_{25}H_{36}N_2$ calcd 364.2879, found 364.2873.

Theonelladin D (2). Theonelladin D (**2**) was obtained in 90% yield from the detosylation of compound **32** using procedure A: ^1H NMR ($CDCl_3$) δ 1.25 (br s, 18 H), 1.47 (m, 2 H), 1.60 (m, 2 H), 2.43 (s, 3 H), 2.56 (t, $J = 7.5$ Hz, 2 H), 2.59 (t, $J = 7.5$ Hz, 2 H), 7.19 (dd, $J = 7.5$, 4.8 Hz, 1 H), 7.48 (d, $J = 7.8$ Hz, 1 H), 8.43 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.3, 29.1, 29.4, 29.6, 29.8, 29.9, 31.1, 33.0, 36.5, 52.2, 123.1, 135.7, 137.9, 147.1, 149.9 (four peaks missing due to overlap); IR (neat) 3301 (N−H), 3081, 3025, 2924, 2852, 1574, 1465, 1369, 1126 cm^{-1}; HRMS for $C_{19}H_{33}N_2(M^+ - H)$ calcd 289.2644, found 289.2642.

General Procedure for the Hydrogenation and Debenzylation of Allylic Benzylamines. To 1.0 equiv of an allylic benzylamine in MeOH (0.05−0.1 M solution) was added 0.35 equiv of Pearlman's catalyst (20% $Pd(OH)_2/C$). The resulting mixture was flushed with H_2 (1 atm) at room temperature for 2−4 h. To the mixture was added 5.0 equiv of NH_4O_2CH. The mixture was heated at 65−70 °C for 10−20 min. After filtration and removal of the solvent, the product was purified on a silica gel column.

Theonelladin C (1). Theonelladin C (**1**) was obtained in 68% yield from the hydrogenation and debenzylation of compound **29** using the above procedure: ^1H NMR ($CDCl_3$) δ 1.23−1.30 (br m, 18 H), 1.43 (m, 2 H), 1.61 (quintet, $J = 7.5$ Hz, 2 H), 2.60 (t, $J = 7.5$ Hz, 2 H), 2.67 (t, $J = 7.5$ Hz, 2 H), 7.19 (dd, $J = 7.5$, 4.8 Hz, 1 H), 7.47 (d, $J = 7.5$ Hz, 1 H), 8.42 (m, 2 H) (NH_2 peak overlapped); ^{13}C NMR ($CDCl_3$) δ 26.9, 29.1, 29.4, 29.5, 29.6, 31.1, 33.0, 33.8, 42.2, 123.1, 135.8, 138.0, 147.1, 149.9 (four peaks missing due to overlap); IR (neat) 3363 (N−H), 3290 (N−H), 3028, 2927, 2854, 1575, 1466, 1309, 1026 cm^{-1}; HRMS for $C_{18}H_{32}N_2$ calcd 276.2566, found 276.2559.

Niphatesine C (3). Niphatesine C (**3**) was obtained in 70% yield from the hydrogenation and debenzylation of compound **35** using the above procedure: ^1H NMR (CD_3OD) δ 0.93 (d, $J = 6.6$ Hz, 3 H), 1.30−1.40 (br m, 16 H), 1.50 (m, 1 H), 1.66 (m, 2 H), 2.43 (dd, $J = 12.3$, 7.2 Hz, 1 H), 2.60 (dd, $J = 12.3$, 5.7 Hz, 1 H), 2.68 (t, $J = 7.2$ Hz, 2 H), 7.37 (dd, $J = 7.8$, 4.8 Hz, 1 H), 7.71 (d, $J = 7.8$ Hz, 1 H), 8.37 (dd, $J = 4.8$, 1.2 Hz, 1 H), 8.39 (d, $J = 1.2$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.4, 27.0, 29.1, 29.4, 29.5, 29.6, 29.9, 31.1, 33.0, 34.3, 36.2, 48.3, 123.1, 135.7, 137.9, 147.1, 149.9 (one peak missing due to overlap); IR (neat) 3365 (N−H), 3300 (N−H), 3025, 2925, 2853, 1574, 1464, 1026 cm^{-1}; HRMS for $C_{18}H_{31}N_2$ ($M^+ - H$) calcd 275.2487, found 275.2480.

Compounds 10 (Xestamine D) and 37. To 39 mg of a mixture of compounds **36a** and **36b** (91:9) in 3 mL of 95% EtOH was added 7.7 mg of 5% Pd/C. The resulting mixture was stirred and flushed with H_2 (1 atm) at room temperature for 6 h. After filtration and removal of the solvent, compounds **10** and **37** were obtained in 92% combined yield: ^1H NMR ($CDCl_3$) δ 1.25−1.30 (br m, 20 H), 1.58 (m, 4 H), 2.56 (s, 3 H), 2.60 (m, 4 H), 3.51 (s, 3 H), 7.19 (dd, $J = 7.5$, 4.8 Hz, 1 H), 7.48 (d, $J = 7.5$ Hz, 1 H), 8.43 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.3, 27.4, 29.1, 29.4, 29.6, 31.1, 33.0, 45.2, 60.0, 61.0, 123.1, 135.7, 137.9, 147.0, 149.9 (six peaks missing due to overlap); IR (neat) 3082, 3026, 2923, 2853, 1576, 1461, 1048 cm^{-1}; HRMS for $C_{21}H_{38}N_2O$ calcd 334.2984, found 334.2992.

Compounds 41a and 41b. To a 1 dram vial with a stirring bar were added 0.5 mmol of 3-iodopyridine, 1.0 mmol of 2-methyl-11-dodecen-1-ol, 5 mol % of $Pd(OAc)_2$, 1.0 mmol of n-Bu_4NCl, 0.5 or 1.0 mmol of LiCl, 1.25 mmol of LiOAc, and 1 mL of DMF. The vial was capped with a screw-cap containing a Teflon liner. The resulting mixture was stirred at 65 °C for 5 days. The mixture was then allowed to cool to room temperature. After removal of the solvent, the residue was purified by flash chromatography on a silica gel column and compounds **41a** and **41b** were obtained as an inseparable 86:14 mixture of isomers in 64% yield: ^1H NMR ($CDCl_3$) δ 1.08 (d, $J = 6.9$ Hz, 3 H), 1.09 (d, $J = 6.9$ Hz, 3 H, **41b**), 1.19−1.41 (m, 14 H), 1.56−1.74 (m, 4 H), 2.35 (m, 1 H), 2.63 (t, $J = 6.9$ Hz, 2 H), 7.20 (dd, $J = 7.5$, 5.1 Hz, 1 H), 7.49 (dt, $J = 7.5$, 1.8 Hz, 1 H), 8,44 (s, 2 H); IR (neat) 3120, 2933, 2512, 1735, 1476, 1120, 954 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 15.4, 18.3 (overlap), 22.0, 29.1, 29.3, 29.4, 31.1, 33.0, 43.9, 76.4, 123.2, 135.8, 138.0, 147.1, 149.9, 203.1. HRMS for $C_{18}H_{29}NO$ calcd 275.2034, found 275.2033.

Ikimine A (6). To an aqueous solution of 93.5 mg (0.25 mmol) of **41a** and **41b** were added 23.0 mg (0.28 mmol) of methoxylamine hydrochloride and 37.4 mg (0.28 mmol) of $NaOAc{\cdot}3H_2O$ until the solution cleared. After 20 h of reflux, the solution was extracted three times with ether. The ether layer was washed three times with 5% aqueous $NaHCO_3$ and once with water and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography on a silica gel column. A mixture of (*E*)- and (*Z*)-isomers was obtained as a liquid in 79% yield. (*E*)-Isomer: ^1H NMR ($CDCl_3$) δ 1.05 (d, $J = 7.5$ Hz, 3 H), 1.26 (m, 16 H), 1.62 (m, 2 H), 2.33 (ddq, $J = 7.5$, 7.5 Hz, 6.8 Hz, 1 H), 2.60 (t, $J = 7.5$ Hz, 2 H), 3.81 (s, 3 H), 7.18−7.22 (m, 2 H), 7.49 (br d, $J = 7.8$ Hz, 1 H), 8.44 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.3, 27.1, 29.2, 29.4, 29.5 (three carbon peaks), 29.6, 31.2, 33.0, 34.4, 34.8, 61.2, 123.3, 135.8, 138.0, 147.2, 149.9, 156.8. (*Z*)-Isomer: ^1H NMR ($CDCl_3$) δ 0.99 (d, $J = 7.5$ Hz, 3 H), 1.26 (m, 16 H), 1.62 (m, 2 H), 2.60 (t, $J = 7.5$ Hz, 2 H), 2.97 (ddq, $J = 7.5$, 7.5, 6.8 Hz, 1H), 3.84 (s, 3 H), 6.38 (d, $J = 7.5$ Hz, 1 H), 7.21 (m, 1 H), 7.49 (br d, $J = 7.8$ Hz, 1 H), 8.44 (br s, 2 H); IR (neat) 3021, 2976, 2431, 1630, 1105, 1066, 967 cm^{-1}; HRMS for $C_{19}H_{32}N_2O$ calcd 304.2515, found 304.2507.

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Supporting Information Available: Preparation and characterization of starting materials **19**, **20**, **32**, **38**, and **39**; characterization data for compounds **14a/b**, **17a/b**, **18a/b**, **23a**, **26**, and **27**; and copies of ^1H NMR and ^{13}C NMR spectra for compounds **1**−**3**, **10**, **14a/b**, **17a/b**, **18a/b**, **21a/b**, **23a**, **26**, **27**, **28a**, **29**, **31a**, **32**, **34a**, **35**, **36a/b**, and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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