JOC The Journal of Organic Chemistry

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Total Synthesis of the Cytotoxic Anhydrophytosphingosine Pachastrissamine (Jaspine B)

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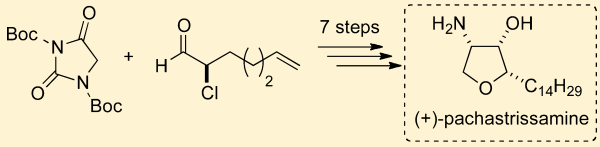
Supporting Information

ABSTRACT: A short, 8-step synthesis of the marine natural product pachastrissamine has been developed that relies on a diastereoselective aldol reaction between a suitably protected hydantoin and an optically enriched α-chloroaldehyde. This synthetic route provides new opportunities for exploring structure activity relationships within this family of natural products.



Pachastrissamine (**1**), also known as jaspine B, is a naturally occurring anhydrophytosphingosine that possesses a tetrahydrofuran core[1] and was first isolated from the Okinawan marine sponge *Pachastrissa* sp. in 2002 by Higa.[2] More recently, Debitus and co-workers reported the isolation of **1** along with a related anhydrophytosphingosine from the Vanuatuan marine sponge *Jaspis* sp. and assigned these compounds the common names jaspine A (**2**) and jaspine B (**1**) (Figure 1).[3] The all-*cis*

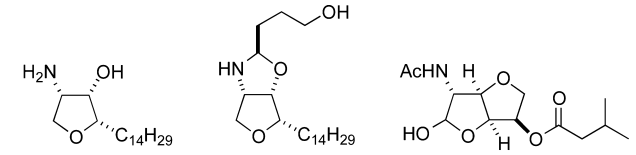
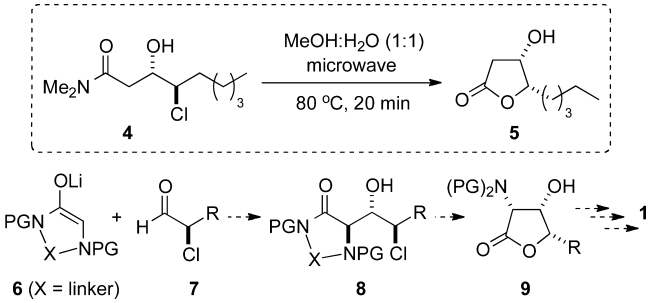


Figure 1. Anhydrophytosphingosines **1** and **2** and furanodictine A (**3**).

trisubsituted tetrahydrofuran ring and absolute configuration (2*S*,3*S*,4*S*) of **1** were assigned by a combination of detailed NMR spectroscopic studies, mass spectral analysis, and chemical derivatization (e.g., formation of MTPA monoamides).[2] Importantly, pachastrissamine exhibited submicromolar cytotoxicity against P388, A549, HT29, MEL28, and HeLa cell lines and represents a potential lead for cancer therapy.[2−4] More recent studies demonstrated that pachastrissamine inhibits the activity of sphingomyelin synthase and consequently increases intracellular ceramide levels, resulting in apoptosis in tumor cells by a caspase-dependent pathway.[5] Owing to its potential importance as a lead for cancer therapy, considerable effort has been devoted to the synthesis of pachastrissamine.[6−8] Presently, more than 25 syntheses of **1** have been reported; however, many of the synthetic strategies are lengthy (ranging from 9 to 19 steps) and have limited ability to access analogues or related natural products (e.g., furanodictine A (**3**))[9] due to their reliance on carbohydrates or amino acids as chiral pool starting materials.

Previously, we have demonstrated that 1,2-*anti*-configured β-ketochlorohydrins can be accessed in a straightforward manner from the reaction of lithium enolates derived from methyl ketones with α-chloroaldehydes.[10] In a single example, it was also shown that microwave-assisted heating the β-amidochlorohydrin **4** in a mixture of CH_3OH-H_2O afforded the β-hydroxy-γ-lactone **5** in excellent yield (Scheme 1).[11] While our

Scheme 1. Synthesis of γ-Lactone 5 and a Synthetic Strategy for Pachastrissamine (1) and Analogues



efforts to date have focused almost exclusively on the reaction of enolates derived from methyl ketones with α-chloroaldehydes,[12] we endeavored to extend this methodology to the preparation of aminotetrahydrofuranols, including pachastrissamine (**1**). As outlined in Scheme 1, it was envisaged that the reaction of a conformationally constrained α-aminoenolate (e.g., **6**) with an α-chloroaldehyde (e.g., **7**) would give rise to an *anti-anti*-aminochlorohydrin (e.g., **8**) based on Evans-Cornforth type stereodirecting effect of the chlorine atom[13] and the progression of the reaction through a chairlike 6-membered ring transition structure.[14] A subsequent thermal cyclization would then provide direct access to α-amino-β-hydroxy-γ-lactones (e.g., **9**) and serve as a launching point for the preparation of pachastrissamine and analogues of this potentially important natural product. Notably, and in contrast to chiral pool syntheses of pachastrissamine, this approach

Received: June 20, 2013
Published: August 6, 2013

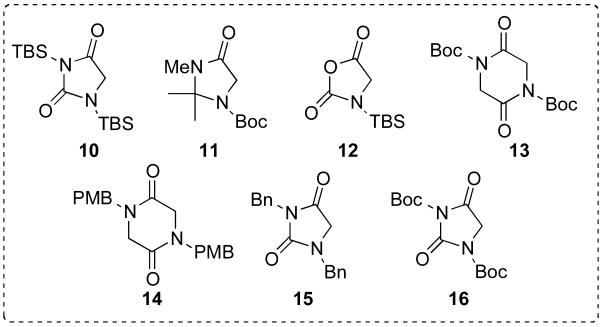
dx.doi.org/10.1021/jo4013223 | J. Org. Chem. 2013, 78, 8208−8213

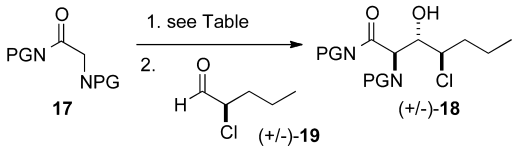
would rely on a single chlorine atom introduced via organocatalytic asymmetric α-chlorination[12] to control the relative stereochemistry of the amino alcohol function in **1**.[15]

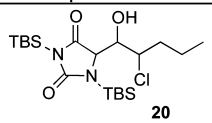
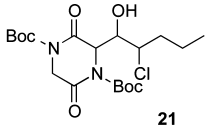
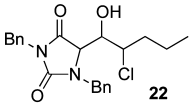
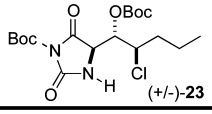
As summarized in Table 1, these studies initiated with an investigation of the lithium aldol reaction between a small collection of α-amino lactams/lactones **10**-**16**[16] and α-chloropentanal (**19**).[12a] As indicated in entry 1, treatment of the TBS-protected hydantoin **10** with freshly prepared lithium diisopropylamide, followed by slow addition of the α-chloroaldehyde **19** afforded the desired aldol adduct in 50% yield albeit with low diastereoselectivity (dr = 1:1). Unfortunately, coupling of the lithium enolates derived from compounds **11** or **12** with α-chloroaldehyde **19** under the same conditions failed to provide detectable amounts of the corresponding chlorohydrin (entries 2 and 3). Similarly, reaction of the protected diketopiperazines **13** and **14** with **19** provided only small amounts (<10%) of the corresponding aldol adducts (entries 4 and 5). Based on the modest success obtained with the TBS protected hydantoin **10**, we next evaluated the benzyl- and Boc-protected analogues **15** and **16**, respectively. As indicated in entries 6 and 7, these hydantoin derivatives reacted with α-chloropentanal to provide the desired β-amidochlorohydrins **22** and **23** in good yield and diastereoselectivity. In the latter example, formation of **23** also involves a 1,3-migration of a Boc protecting group[17] and the β-amidochlorohydrin **23** could be isolated in good yield. It is noteworthy that this straightforward strategy for the synthesis of **23** could also be exploited for the preparation of various β-hydroxy-α-amino acids by radical reduction of the chloromethine function,[18] or more elaborate amino acid derivatives through displacement of the chloride with nitrogen or oxygen nucleophiles.

Following the successful preparation of the β-amidochlorohydrins **20**, **22**, and **23**, we next investigated the thermal cyclization of these compounds.[11] Fortunately, while attempts to effect cyclization of the β-amidochlorohydrins **20** or **22** at temperatures ranging from 50 °C to reflux in a variety of solvents (e.g., H_2O, CH_3OH, DMSO, MeCN, pH 7 buffered H_2O) led largely to their decomposition,[11] heating of the β-amidochlorohydrin **23** in a mixture of CH_3OH–H_2O afforded the γ-lactone **27**, which could be isolated in 15% yield along with the fully deprotected β-amidochlorohydrin **28** (Table 2, entry 1). Surprisingly, we were unable to convert the chloroamide **28** into the corresponding lactone even after heating at reflux for more than 24 h in H_2O, which resulted in complete recovery of the starting material. Together, these results suggest that formation of the desired γ-lactone **27** most likely proceeds via initial deprotection of the Boc-protected alcohol in **23** to provide the chlorohydrin **24** (Scheme 2). A second deprotection would then afford the chloroamide **28**, while a structural rearrangement from the hydantoin **24** to carbamate **25** is a necessary step preceding the formation of γ-lactone **27**. In an effort to optimize the fortuitous rearrangement of hydantoin **24** to carbamate **25** necessary for the formation of lactone **27**, we screened a variety of solvents and temperatures for this reaction (Table 2). As indicated in entries 2 and 3, heating of chlorohydrin **23** in dimethyl carbonate or DMSO at 60 °C afforded none of the desired γ-lactone **27**. Interestingly, formation of the γ-lactone **27** was significantly enhanced when the reaction was heated in a mixture of

Table 1. Lithium Aldol Reactions between α-Chloroaldehyde (±)-19 and Different α-Amino Amides





entry	lactam	base[a]	product	yield (dr)[b]
1	**10**	A	 **20**	50% (1:1)[c]
2	**11**	A	nd[d]	0
3	**12**	A	nd[d]	0
4	**13**	A	 **21**	<10%
5	**14**	B	nd[d]	0
6	**15**	B	 **22**	40% (>20:1)[c]
7	**16**	B	 (+/-)-**23**	61% (10:1:1:1)[e,f]

[a]Conditions: (A) LDA, THF, −78 °C, 30 min, then **19**; (B) LiHMDS, THF, −78 °C, 30 min, then **19**. [b]Yield and diastereomeric ratio determined by analysis of ^{1}H NMR spectra recorded on crude reaction products with internal standard. [c]The relative stereochemistry was not determined. [d]No product detected. [e]Products partially decompose during purification by flash column chromatography. [f]Major diastereomer is **23** (isolated in 45% yield).

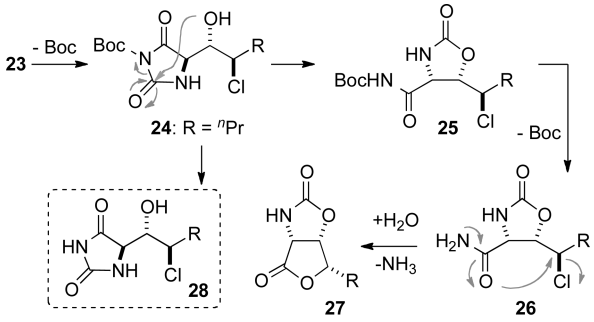
Table 2. Reaction Conditions for Formation of the γ-Lactone 27 from 23

entry	solvent(s)	temp[a] (°C)	**27**:**28**[b] (% yield)[c]
1	H_2O–CH_3OH (1:1)	60	1:3 (62)
2	dimethyl carbonate	60	nd[d]
3	DMSO	60	nd[d]
4	H_2O–CH_3OH (1:1)	100	1.7:1
5	H_2O-^{t}BuOH (1:1)	100	1.1:1
6	H_2O–CF_3CH_2OH (1:1)	100	1.2:1
7[e]	H_2O–CH_3OH (1:1.2)	100	2.7:1 (58)

[a]Reaction carried out in a sealed tube in an oil bath. [b]Determined by analysis of ^{1}H NMR spectra recorded on crude reaction mixture. [c]Combined isolated yield. [d]No product detected. [e]Reaction carried out in a microwave reactor.

dx.doi.org/10.1021/jo4013223 | J. Org. Chem. 2013, 78, 8208–8213

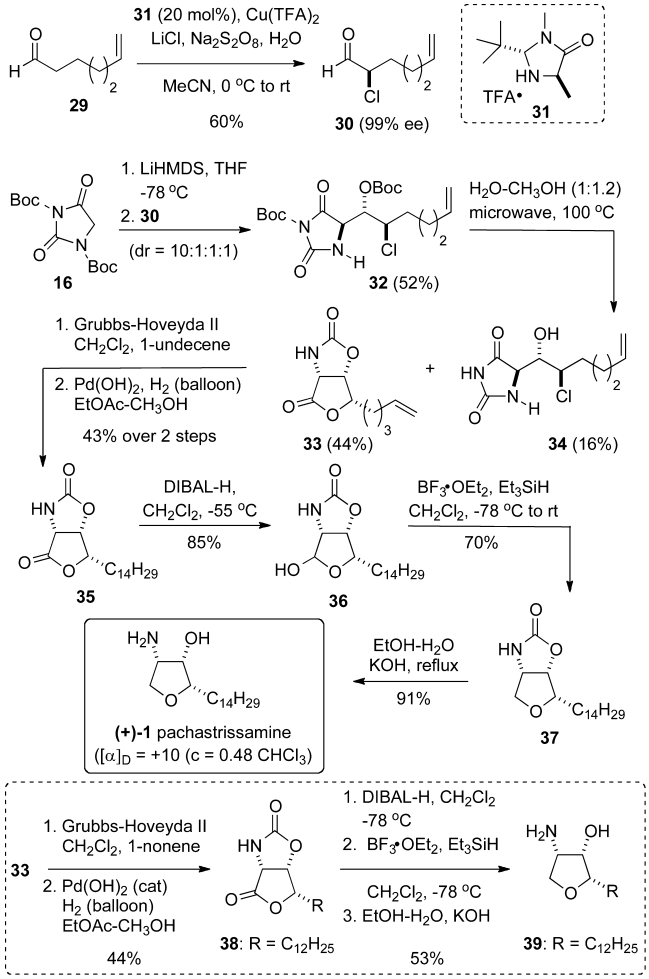
Scheme 2. Potential Mechanism for the Formation of γ-Lactone 27



$CH_3OH–H_2O$ at 100 °C (entry 4). Further increases to the reaction temperature (eg., 120 °C in a microwave reactor) in $CH_3OH–H_2O$ (1:1) did not alter the ratio of γ-lactone **27** to β-amidochlorohydrin **28**. To further examine this process, a series of solvent mixtures were examined. As indicated in entries 5 and 6, heating the β-amidochlorohydrins **23** in $H_2O–{}^tBuOH$ or $H_2O–CF_3CH_2OH$ under the same reaction conditions failed to improve on the results obtained in $CH_3OH–H_2O$ (1:1). After screening the reaction in several different mixtures of $CH_3OH–H_2O$, we eventually found that the ratio of γ-lactone **27** to β-amidochlorohydrin **28** could be optimized to 2.7:1 in a $H_2O–CH_3OH$ mixture of 1:1.2 (entry 7). This latter reaction could be carried out in a microwave reactor and was complete in 20 min, affording the desired γ-lactone **27** in 40% yield accompanied with a 18% yield of the deprotected β-amidochlorohydrin **28** (entry 7).

Having developed a short synthetic route to the γ-lactone **27**, we focused our efforts on applying this strategy to the total synthesis of (+)-pachastrissamine (**1**). As depicted in Scheme 3, the synthesis of **1** commenced with the asymmetric α-chlorination of 6-heptenal (**29**) following the procedure reported by MacMillan.[12c] While the chlorination of hexadecanal would eliminate two steps from the total synthesis (see below), the choice of 6-heptenal provides opportunities for the late stage production of pachastrissamine analogues through cross metathesis.[19] A subsequent aldol reaction between the Boc-protected hydantoin **16** and the optically enriched α-chloroaldehyde **30** afforded a mixture of chlorohydrins in good yield (68%) and diastereoselectivity (dr = 10:1:1:1), from which the desired aldol adduct could be isolated in 52% yield. Cyclization of the chlorohydrin **32** using the optimized reaction conditions (Table 2, entry 7) produce a 2.7:1 mixture of the desired the γ-lactone **33** and the chlorohydrin **34**, in 60% yield. Cross-metathesis of the purified the γ-lactone **33** with 1-undecene catalyzed by the second-generation Grubbs–Hoveyda catalyst[20] afforded the corresponding tetradecene, which was directly hydrogenated to give the lactone **35** in 43% yield over the two steps. Reduction of the lactone function involved treatment of compound **35** with DIBAL-H followed by reaction of the resulting mixture of lactols with Et_3SiH and $BF_3{\cdot}OEt_2$[21] to afford the cyclic carbamate **37**.[6b] Finally, the carbamate was removed under basic conditions to afford (+)-pachastrissamine (**1**) in 91% yield. The spectroscopic data (^1H NMR, ^{13}C NMR, HRMS, and IR) of our synthetic pachastrissamine (**1**) were in complete agreement with those reported in the literature,[6c] and the specific rotation was consistent with that reported ($[\alpha]_D$ = +10 (*c* = 0.48 $CHCl_3$)).[6c] To further demonstrate the potential of this synthetic route for

Scheme 3. Total Synthesis of (+)-Pachastrissamine (1) and the Dodecyl Analogue 39



providing access to structural analogues of pachastrissamine, the γ-lactone **33** was also converted into the truncated derivative **39** (i.e., dodecyl analogue) following an identical sequence of reactions that initiated with cross metathesis of **33** with 1-nonene (see inset, Scheme 3).

In conclusion, we have developed a short (eight step, 5% overall yield) asymmetric synthesis of pachastrissamine (**1**) that relies on the diastereoselective aldol reaction between a Boc-protected hydantoin and an optically enriched α-chloroaldehyde to secure the correctly configured core of **1**. A fortuitous Boc protecting group migration proved key in the thermal cyclization of this material, which proved to be extremely sensitive to both temperature and solvent. Notably, the present synthesis compares well with those reported and, as demonstrated through the production of the dodecyl analogue **39**, should be readily adapted to the production of analogues of pachastrissamine through cross-metathesis or initiation of the process with other readily available α-chloroaldehydes (e.g., **27**, Scheme 2). Furthermore, the ready access to optically enriched β-amidochlorohydrins afforded by this process may also prove useful for the production of β-hydroxyamino acids and other more elaborate amino acid derivatives.

EXPERIMENTAL SECTION

Preparation of (±)-Hydantoin 23. To a cold (−78 °C), stirred solution of hexamethyldisilazane (1.2 mL, 5.5 mmol) in THF (4.0

dx.doi.org/10.1021/jo4013223 | J. Org. Chem. 2013, 78, 8208–8213

mL) was added *n*-butyllithium (2.59 M solution in hexanes, 2.0 mL, 5.1 mmol) dropwise. The resulting mixture was allowed to warm to rt slowly over 15 min and then added dropwise via cannula to a cold (−78 °C), stirred solution of Boc-protected hydantoin **16** (1.4 g, 4.6 mmol) in THF (34 mL). After the mixture was stirred for 45 min, (±)-2-chloropentanal (**19**) (674 mg, 5.5 mmol) in THF (4.0 mL) was added dropwise, and the resulting mixture was stirred for an additional 1.2 h. After this time, the reaction was treated with saturated aqueous solution of sodium dihydrogen phosphate (10 mL) and diluted with EtOAc (60 mL) and H_2O (60 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash chromatography (silica gel, hexanes−EtOAc 3:1) afforded hydantoin **23** (876 mg, 45%) as a colorless oil. The stereochemical assignment for compound **23** was based on analysis of 1D NOESY spectra and comparison of its spectral data with that recorded on the structurally related hydantoin **35** (see below). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.68 (br s, 1H), 5.11 (dd, 1H, J = 5.2, 2.1 Hz), 4.39 (dd, 1H, J = 2.1, 1.5 Hz), 4.14 (m, 1H), 1.81−1.64 (m, 2H), 1.57 (s, 9H), 1.53−1.41 (m, 2H), 0.94 (t, 3H, J = 7.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.8, 152.2, 152.1, 145.6, 85.7, 84.1, 75.3, 61.2, 56.5, 36.0, 27.7, 27.5, 19.3, 13.3. IR (neat): 3312, 2980, 2936, 2876, 1813, 1774, 1725, 1274, 1153 cm^{-1}. HRMS: $[M + Na]^+$ calcd for $C_{18}H_{29}ClN_2NaO_7$ 443.1556, found 443.1584.

Preparation of (±)-γ-Lactone 27. To an 80 mL vial containing hydantoin **23** (876 mg, 2.1 mmol) was added 1:1.2 mixture of deionized H_2O−CH_3OH (1:1.2, 25.6 mL), and the vial was sealed in a CEM Discover LabMate microwave reactor. The reaction mixture was then heated for 20 min at 100 °C (as monitored by a vertically focused IR temperature sensor). After this time, the mixture was diluted with EtOAc (30 mL) and H_2O (30 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 30 mL), and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash chromatography (silica gel, CH_2Cl_2−CH_3OH 20:1) afforded γ-lactone **27** as a white solid (157 mg, 40%, mp = 136−138 °C) and hydantoin **28** (82 mg, 18%). Data for γ-lactone **27**. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.68 (br s, 1H), 5.21 (dd, 1H, J = 4.5, 7.6 Hz), 4.66 (m, 1H), 4.44 (d, 1H, J = 7.5 Hz), 1.96−1.81 (m, 2H), 1.57−1.49 (m, 2H), 1.01 (t, 3H, J = 7.4 Hz). ^{13} C NMR (150 MHz, $CDCl_3$) δ: 172.5, 156.7, 82.2, 77.0, 54.9, 30.9, 18.5, 13.7. IR (neat): 3268, 2962, 2877, 1753, 1710, 1222, 968 cm^{-1}. HRMS: $[M + H]^+$ calcd for $C_8H_{12}NO_4$ 186.0761, found 186.0741. Data for hydantoin **28**. ^{1}H NMR (600 MHz, DMSO) δ: 5.87 (d, 1H, J = 7.5 Hz), 4.35 (t, 1H, J = 1.4 Hz), 4.00 (dt, 1H, J = 2.7, 9.8 Hz), 3.69 (ddd, 1H, J = 1.4, 7.5, 9.4 Hz), 1.54 (m, 2H), 1.36 (m, 2H), 0.90 (t, 3H, J = 7.2 Hz). ^{13} C NMR (150 MHz, DMSO) δ: 174.8, 158.1, 72.3, 62.2, 60.3, 35.3, 18.5, 13.3. IR (neat): 3263, 2920, 1768, 1716, 1261, 1147 cm^{-1}. HRMS: $[M + H]^+$ Calcd for $C_8H_{14}ClN_2O_3$ 221.0725; Found 221.0719.

Preparation of (+)-(*R*)-2-Chlorohept-6-enal (30). To a cold (−10 °C), stirred solution of LiCl (1.91 g, 0.045 mol), copper(II) trifluoroacetate hydrate (4.36 g, 0.015 mol), sodium persulfate (7.18 g, 0.030 mol), and H_2O (1.2 mL, 0.066 mol) in acetonitrile (130 mL) was added imidazolidinone catalyst **31** (1.72 g, 6.0 mmol). After the mixture was stirred for 5 min, 6-heptenal (**29**) (3.38 g, 0.030 mol) in acetonitrile (20 mL) was added dropwise. The resulting mixture was stirred at −10 °C for 2 days, after which EtOAc (70 mL) and H_2O (70 mL) were added. The phases were separated, and the aqueous phase was washed with EtOAc (3 × 70 mL). The combined organic phases were washed with brine (70 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash chromatography (silica gel, 1:1 CH_2Cl_2−pentane) afforded (+)-(*R*)-2-chlorohept-6-enal (**30**) as a colorless oil (2.60 g, 60%, ee >99.0%). $[\alpha]^{25}_D$: +37 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.49 (d, 1H, J = 2.4 Hz), 5.77 (m, 1H), 5.03 (m, 1H), 5.00 (m, 1H), 4.16 (ddd, 1H, J = 8.1, 5.4, 2.4 Hz), 2.10 (m, 2H), 2.00 (m, 1H), 1.84 (m,1H), 1.64 (m, 1H), 1.55 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 195.6, 137.9, 115.9, 64.2, 33.2, 31.7, 25.1. IR (neat): 2923, 2855, 1736, 1460, 913, 744 cm^{-1}. HRMS: $[M + H]^+$ calcd for $C_7H_{12}ClO$ 147.0566, found 147.0571.

Preparation of Hydantoin 32. To a cold (−78 °C), stirred solution of hexamethyldisilazane (1.4 mL, 6.6 mmol) in THF (6.0 mL) was added *n*-butyllithium (2.66 M solution in hexanes, 2.3 mL, 6.0 mmol) dropwise. The resulting mixture was allowed to warm to rt slowly over 15 min and then added dropwise via cannula to a cold (−78 °C), stirred solution of Boc-protected hydantoin **16** (1.65 g, 5.5 mmol) in THF (36 mL). After the mixture was stirred for 45 min, (+)-(*R*)-2-chlorohept-6-enal (**30**) (886 mg, 6.0 mmol) in THF (4.0 mL) was added dropwise, and the resultant mixture was stirred for an additional 1.2 h. After this time, the reaction mixture was treated with saturated aqueous sodium dihydrogen phosphate (10 mL) and diluted with EtOAc (60 mL) and H_2O (60 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash chromatography (silica gel, hexanes−EtOAc 3:1) afforded the hydantoin (**32**) as a white solid (1.28 g, 52%). $[\alpha]^{25}_D$: −12 (c 0.65, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.76 (m, 1H), 5.62 (br s, 1H), 5.12 (dd, 1H, J = 2.1, 5.2 Hz), 5.01 (m, 2H), 4.39 (br s, 1H), 4.12 (m, 1H), 2.10 (m, 2H), 1.84 (m, 1H), 1.74 (m, 1H), 1.57 (s, 9H), 1.51−1.54 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7, 152.2, 152.1, 145.6, 137.5, 115.6, 85.8, 84.1, 75.2, 61.3, 56.5, 33.4, 32.8, 27.8, 27.5, 25.1. IR (neat): 3307, 2981, 2936, 1813, 1774, 1725, 1370, 1274, 1153 cm^{-1}. HRMS: $[M + Na]^+$ calcd for $C_{20}H_{31}ClN_2NaO_7$ 469.1712, found 469.1707.

Preparation of γ-Lactone 33. To the 80 mL vial containing hydantoin **32** (1.25 g, 2.7 mmol) was added a mixture of deionized H_2O−CH_3OH (1:1.2, 36 mL), and the vial was sealed in a CEM Discover LabMate microwave reactor. The reaction mixture was then heated for 20 min at 100 °C (as monitored by a vertically focused IR temperature sensor). After this time, the mixture was diluted with EtOAc (60 mL) and H_2O (60 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL), and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash chromatography (silica gel, CH_2Cl_2−CH_3OH 20:1) afforded the γ-lactone **33** as an off-white solid (250 mg, 44%; mp = 108−111 °C). $[\alpha]^{20}_D$: −13 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.79 (m, 1H), 5.63 (s, 1H), 5.21 (dd, 1H, J = 4.5, 7.4 Hz), 5.02 (m, 2H), 4.65 (m, 1H), 4.44 (dd, 1H, J = 0.71, 7.4 Hz), 2.15 (m, 2H), 1.95 (m, 1H), 1.88 (m, 1H), 1.60 (m, 2H). ^{13} C NMR (150 MHz, $CDCl_3$) δ: 172.2, 156.3, 137.5, 115.6, 82.3, 76.9, 54.7, 33.2, 28.4, 24.4. IR (neat): 3251, 2925, 1774, 1726, 1365, 1218, 1110, 964, 655 cm^{-1}. HRMS: $[M + Na]^+$ calcd for $C_{10}H_{13}NNaO_4$ 234.0737, found 234.0763.

Preparation of γ-Lactone 35. To a stirred solution of 1-undecene (0.24 mL, 1.2 mmol) in CH_2Cl_2 (7.5 mL) was added γ-lactone **33** (31 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) followed by the second-generation Grubbs−Hoveyda catalyst (17 mg, 0.027 mmol). Nitrogen was bubbled through the mixture for 5 min, after which time the mixture was heated to reflux and maintained at this temperature for 3 h. The reaction mixture was then cooled to rt, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:1 hexanes−EtOAc) to give the cross-metathesis product as an off-white solid (25 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.28 (br s, 1H), 5.55−5.29 (m, 2H), 5.20 (dd, 1H, J = 4.2, 7.0 Hz), 4.65 (m, 1H), 4.47 (d, 1H, J = 7.3 Hz), 2.28−1.79 (m, 6H), 1.66−1.46 (m, 2H), 1.46−1.23 (m, 16H), 0.88 (t, 3H, J = 6.7 Hz).

To a stirred solution of the cross-metathesis product (25 mg, 0.073 mmol) in EtOAc−CH_3OH (1:1, 3.6 mL) was added $Pd(OH)_2$ (5.4 mg). Hydrogen was bubbled through the mixture for 30 min, and then the reaction was kept under hydrogen atmosphere for 1.5 h. After this time, the mixture was filtered through a pad of Celite and concentrated to afford γ-lactone **35** as an off-white solid (22 mg, 43% over two steps; mp = 146−148 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.97 (br s, 1H), 5.21 (dd, 1H, J = 4.4, 7.4 Hz), 4.65 (m, 1H), 4.45 (d, 1H, J = 7.4 Hz), 1.99−1.80 (m, 2H), 1.48 (m, 1H), 1.41−1.20 (m, 23H), 0.88 (t, 3H, J = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.4, 156.6, 82.6,

dx.doi.org/10.1021/jo4013223 | J. Org. Chem. 2013, 78, 8208−8213

77.0, 54.9, 31.9, 29.7, 29.7, 29.6, 29.6, 29.6, 29.6, 29.5, 29.3, 29.2, 29.0, 25.2, 22.7, 14.1. IR (neat): 3260, 2957, 2918, 2850, 1778, 1724, 1217 cm^{-1}. HRMS: $[M + H]^+$ calcd for $C_{19}H_{34}NO_4$ 340.2482, found 340.2462.

Preparation of Lactol 36. To a stirred solution of γ-lactone **35** (31 mg, 0.090 mmol) in CH_2Cl_2 (4.4 mL) at −55 °C was slowly added a solution of diisobutylaluminum hydride (1.0 M in THF, 0.32 mL, 0.32 mmol), and the resulting mixture was stirred for 12 h. An additional amount of diisobutylaluminum hydride (1.0 M in THF, 0.32 mL, 0.32 mmol) was then added, and the resulting mixture was stirred for 9 h at −55 °C. The excess reagent was then quenched by addition of 1 M HCl (1.5 mL), and the resulting mixture was diluted with EtOAc (10 mL), H_2O (5 mL), and brine (5 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography (silica gel, EtOAc-hexanes 7:3) afforded lactol **36** as a white solid (26 mg, 85%, mp = 94−96 °C). ^1H NMR (400 MHz, $CDCl_3$) δ: 6.54 (br s, 1H), 5.30 (br s, 1H), 5.03 (dd, 1H, *J* = 3.6, 7.2 Hz), 4.27−4.20 (m, 2H), 3.46 (br s, 1H), 1.74 (m, 2H), 1.48−1.41 (m, 24H), 0.88 (t, 3H, *J* = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 100.9, 80.5, 80.1, 62.8, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.3, 28.0, 26.0, 22.7, 14.1. IR (neat): 3428, 3304, 2918, 2850, 1762, 1733, 1071, 1014 cm^{-1}. HRMS: $[M + H]^+$ calcd for $C_{19}H_{36}NO_4$ 342.2639, found 342.2650.

Preparation of Carbamate 37. To a cold (−78 °C), stirred solution of lactol **36** (26 mg, 0.076 mmol) and triethylsilane (0.12 mL, 0.76 mmol) in CH_2Cl_2 (3.6 mL) was added $BF_3{\cdot}OEt_2$ (0.050 mL, 0.38 mmol), and the reaction mixture was allowed to warm to rt and stir for an additional 19.5 h. After this time, the reaction was treated with saturated aqueous solution of $NaHCO_3$ (5 mL) and diluted with EtOAc (10 mL). The phases were separated, and the aqueous phase was washed with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography (7:3 EtOAc−hexanes) provided the carbamate **37** as a white solid (8.0 mg, 32%; mp = 112−115 °C). Additional amounts of the starting lactol **36** (11 mg) were also isolated and redissolved in CH_2Cl_2 (5.0 mL). The resulting solution was cooled to 0 °C, and both Et_3SiH (0.10 mL, 0.63 mmol) and $BF_3{\cdot}OEt_2$ (0.040 mL, 0.30 mmol) were added. The mixture was warmed to rt and allowed to stir for 48 h, after which time additional Et_3SiH (0.10 mL, 0.63 mmol) and $BF_3{\cdot}OEt_2$ (0.040 mL, 0.30 mmol) were added. After a further 48 h, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (5 mL) and diluted with EtOAc (10 mL). The phases were separated, and the aqueous phase was washed with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to give tetrahydrofuran carbamate **37** as a white solid (9.5 mg, 38%). Total isolated yield of carbamate **37** = 70%. $[\alpha]^{20}_D$: +54 (*c* 0.72, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 6.06 (br s, 1H), 4.95 (dd, 1H, *J* = 3.6, 7.4 Hz), 4.37 (dd, 1H, *J* = 3.6, 7.4 Hz), 3.94 (d, 1H, *J* = 10.4 Hz), 3.54−3.48 (m, 2H), 1.83−1.71 (m, 2H), 1.51−1.20 (m, 24H), 0.88 (t, 3H, *J* = 6.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 159.2, 83.2, 80.9, 73.3, 57.1, 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.6, 29.5, 29.3, 28.1, 26.0, 22.7, 14.1. IR (neat): 3330, 3242, 2921, 2848, 1756, 1720, 1070 cm^{-1}. HRMS: $[M + H]^+$ calcd for $C_{19}H_{36}NO_3$ 326.2690, found 326.2686.

Preparation of (+)-Pachastrissamine (1). To a stirred solution of tetrahydrofuran carbamate **37** (7.1 mg, 0.022 mmol) in EtOH (1.5 mL) was added a solution of KOH (1 M in H_2O, 1.2 mL), and the mixture was heated to reflux (85 °C) and maintained at this temperature for 15 h. The reaction mixture was then cooled to rt and diluted with EtOAc (10 mL) and H_2O (5 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification of crude product by flash chromatography (silica gel, $CHCl_3$−CH_3OH−NH_4OH 95:8:1) afforded (+)-pachastrissamine (**1**) as a white solid (5.9 mg, 91%; mp = 83−85 °C, lit.[6c] mp = 89−91 °C). $[\alpha]^{20}_D$: +10 (*c* 0.48, $CHCl_3$). $[\alpha]^{20}_D$: +16 (*c* 0.45, EtOH). ^1H NMR (600 MHz, $CDCl_3$) δ: 3.92 (dd, 1H, *J* = 7.7, 7.7 Hz), 3.87 (m, 1H), 3.73 (m, 1H), 3.65 (m, 1H), 3.52 (dd, 1H, *J* = 7.7, 7.7 Hz), 2.25 (br s, 2H), 1.72−1.59 (m, 2H), 1.47−1.19 (m, 24H), 0.88 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 83.2, 72.3, 71.7, 54.3, 31.9, 29.8, 29.7, 29.7, 29.6, 29.6, 29.6, 29.4, 29.4, 29.3, 26.3, 22.7, 14.1 cm^{-1}. IR (neat): 3341, 2917, 2849, 1583, 1470, 1034 cm^{-1}. HRMS: $[M + H]^+$ calcd for $C_{18}H_{38}NO_2$ 300.2897, found 300.2900.

Preparation of (±)-γ-Lactone 38. To a stirred solution of γ-lactone **33** (20 mg, 0.094 mmol) in CH_2Cl_2 (5.0 mL) was added 1-nonene (0.13 mL, 0.76 mmol) followed by the second-generation Grubbs−Hoveyda catalyst (12 mg, 0.019 mmol). The reaction mixture was heated to reflux and maintained at this temperature for 3 h, after which time the mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:1 hexanes−EtOAc) to give the γ-lactone **38** as a white solid (17 mg, 54%, mp = 158−161 °C). ^1H NMR (600 MHz, $CDCl_3$) δ: 5.59 (s, 1H), 5.46−5.34 (m, 2H), 5.20 (dd, 1H, *J* = 4.4, 7.3 Hz), 4.65 (m, 1H), 4.44 (d, 1H, *J* = 7.3 Hz), 2.10−1.84 (m, 7H), 1.61−1.51 (m, 3H), 1.35−1.23 (m, 14H), 0.87 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 172.2, 156.3, 131.9, 128.6, 82.4, 77.0, 54.9, 32.5, 32.0, 31.8, 29.5, 29.1, 29.1, 28.4, 25.1, 22.6, 14.1. IR (neat): 3344, 2959, 2923, 2854, 1784, 1751, 1242, 1103, 965 cm^{-1}.

To a stirred solution of cross-metathesis product (17 mg, 0.050 mmol) in EtOAc−CH_3OH 1:1 (3.0 mL), was added $Pd(OH)_2$ (3.4 mg), and the resulting mixture was stirred under a hydrogen atmosphere (balloon) for 1.5 h. After this time, the mixture was filtered through a pad of Celite and concentrated. Purification of crude product by flash chromatography (silica gel, 1:1 hexanes−EtOAc) afforded the γ-lactone **38** (14 mg, 82%). ^1H NMR (600 MHz, $CDCl_3$) δ: 5.55 (b, 1H), 5.21 (dd, 1H, *J* = 4.5, 7.5 Hz), 4.64 (m, 1H), 4.44 (dd, 1H, *J* = 0.66, 7.5 Hz), 1.93 (m, 1H), 1.86 (m, 1H), 1.51−1.42 (m, 5H), 1.40−1.34 (m, 3H), 1.32−1.23 (m, 16H), 0.88 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 172.2, 156.3, 82.5, 76.9, 54.8, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 28.9, 25.1, 22.7, 14.1. IR (neat): 3673, 3250, 2981, 2917, 2854, 1777, 1726, 1393, 1219, 1066 cm^{-1}. HRMS: $[M + H]^+$ calcd for $C_{17}H_{30}NO_4$ 312.2200, found 312.2169.

Preparation of the (±)-Dodecyl Analogue of Pachastrissamine (39). To a cold (−78 °C), stirred solution of γ-lactone **38** (28 mg, 0.082 mmol) in CH_2Cl_2 (4.0 mL) was slowly added a solution of diisobutylaluminum hydride (1.0 M in THF, 0.29 mL, 0.29 mmol), and the resulting mixture was stirred for 7 h. The excess reagent was then quenched by addition of 1 M HCl (1.0 mL), and the resulting mixture was diluted with EtOAc (10 mL) and H_2O (10 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography (silica gel, EtOAc−hexanes 2:1) afforded the corresponding lactol (20.5 mg, 72%). ^1H NMR (600 MHz, $CDCl_3$) δ: 5.66 (b, 1H), 5.31 (b, 1H), 5.03 (dd, 1H, *J* = 3.7, 7.2 Hz), 4.25 (m, 1H), 4.22 (d, 1H, *J* = 7.2 Hz), 2.64 (d, 1H, *J* = 7.9 Hz), 1.75 (m, 2H), 1.42 (m, 2H), 1.28 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 158.6, 101.0, 80.4, 80.2, 62.5, 31.9, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 28.0, 25.9, 22.7, 14.1. IR (neat): 3341, 2921, 2852, 1736, 1075 cm^{-1}. HRMS: $[M + H]^+$ calcd for $C_{17}H_{32}NO_4$ 314.2300, found 314.2319.

To a cold (−78 °C), stirred solution of lactol (22 mg, 0.064 mmol) and triethylsilane (0.10 mL, 0.64 mmol) in CH_2Cl_2 (3.0 mL) was slowly added $BF_3{\cdot}OEt_2$ (40 μL, 0.32 mmol), and the reaction mixture was allowed to warm to rt and stir for an additional 16 h. After this time, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (5 mL) and diluted with EtOAc (10 mL). The phases were separated, and the aqueous phase was washed with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide the tetrahydrofuran carbamate (20 mg, 90%). ^1H NMR (500 MHz, $CDCl_3$) δ: 5.10 (s, 1H), 4.96 (dd, 1H, *J* = 3.7, 7.5 Hz), 4.37 (dd, 1H, *J* = 3.9, 7.5 Hz), 3.93 (d, 1H, *J* = 10.3 Hz), 3.55−3.50 (m, 2H), 1.77 (m, 2H), 1.47−1.23 (m, 24H), 0.88 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 158.5, 83.3, 80.9, 73.4, 56.9, 31.9, 29.7, 29.6, 29.6,

dx.doi.org/10.1021/jo4013223 | J. Org. Chem. 2013, 78, 8208−8213

29.5, 29.4, 29.3, 28.1, 26.0, 22.7, 14.1. IR (neat): 2923, 2854, 1747, 1718, 1072 cm^{-1}. HRMS: $[M + H]^+$ calcd for $C_{17}H_{32}NO_3$ 298.2400, found 298.2355.

To a stirred solution of tetrahydrofuran carbamate (12 mg, 0.037 mmol) in EtOH (1.7 mL) was added a solution of KOH (1 M in H_2O, 1.7 mL), and the mixture was heated to reflux and maintained at this temperature for an additional 12 h. The reaction mixture was then cooled to rt and concentrated. Purification of the crude product by flash chromatography (silica gel, $CHCl_3$–CH_3OH–NH_4OH 95:6:1) afforded (±)-dodecyl analogue of pachastrissamine (**39**) as a white solid (9.0 mg, 82%; mp = 74–76 °C). ^1H NMR (400 MHz, $CDCl_3$) δ: 3.92 (dd, 1H, J = 7.3, 8.4 Hz), 3.86 (dd, 1H, J = 3.5, 5.0 Hz), 3.73 (m, 1H), 3.66 (m, 1H), 3.51 (dd, 1H, J = 6.6, 8.4 Hz), 2.02 (br s, 2H), 1.69–1.61 (m, 2H), 1.42–1.22 (m, 24H), 0.88 (t, 3H, J = 6.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 83.2, 72.4, 71.7, 54.2, 31.9, 29.8, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 26.3, 22.7, 14.1. IR (neat): 3675, 3157, 2918, 2850, 1469, 1054 cm^{-1}. HRMS: $[M + H]^+$ calcd for $C_{16}H_{34}NO_2$ 272.2600, found 272.2575.

■ ASSOCIATED CONTENT

Supporting Information

General experimental methods and copies of ^1H and ^{13}C NMR spectra. 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.

■ ACKNOWLEDGMENTS

This work was supported by an NSERC Discovery Grant for R.B., a Michael Smith Foundation for Health Research Career Investigator Award for R.B., a NSERC Postgraduate Scholarship for S.C., and SFU Graduate Fellowships for S.C. and V.D. The authors thank R. Gries for assistance with chiral GC analysis.

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