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Sterically Biased 3,3-Sigmatropic Rearrangement of Chiral Allylic Azides: Application to the Total Syntheses of Alkaloids

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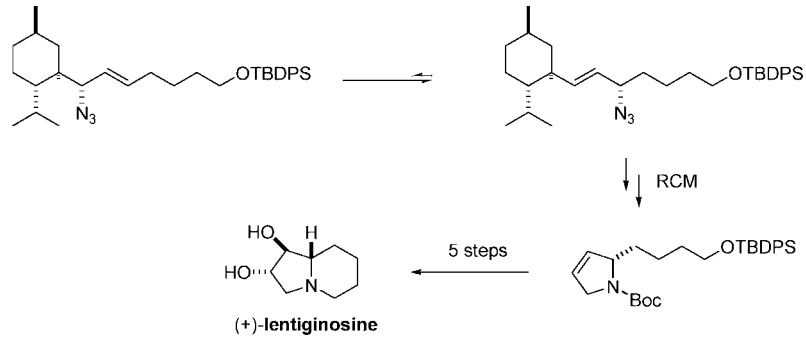

We describe a tandem Mitsunobu/3,3-sigmatropic rearrangement of allylic azides on a chiral auxiliary system that favors one regioisomer thanks to its exceptional steric bias. The sequence may be completed by the oxidative cleavage of the auxiliary or by a ring-closing metathesis reaction that produces a carbo- or heterocycle directly and a recyclable form of the chiral auxiliary. Applications of the methodology to the total synthesis of (+)-coniine, (+)-lentiginosin, and (+)-pumiliotoxin C are reported.

Introduction

The 3,3-sigmatropic rearrangement of azides were first observed in 1960 by Winstein and co-workers.[1] They prepared a 70−30 mixture of 2-azido-2-methyl-3-butene and 1-azido-3-methyl-2-butene that were interconverting fast at room-temperature but were stable for days at −80 °C. Others reported obtaining thermodynamic mixtures of acyclic allylic azides at or lower than room temperature.[2] Cyclic allylic azides, it seems, require higher temperatures to rearrange.[3]

Indeed, most allylic azides exist as mixtures of regioisomers that interconvert rapidly at ambiant temperature, a drawback that has hampered their use in synthesis. VanderWerf and Heasley have noted that, in general, tertiary and secondary allylic azides rearrange more rapidly than primary allylic azides.[4] In addition, the regioisomer with the more substituted alkene was usually thermodynamically favored. A high degree of regioselectivity could be obtained in cases where the double bond was conjugated with an insaturation[5] while some degree of regiochemical control was achieved using competitive reactivity of either the azide or alkene moiety.[6] A chiral scaffold capable of biasing the thermodynamic ratio of regioisomeric allylic azides and lead to useful structural motifs is highly desirable.

We recently reported a novel approach to construct chiral nonracemic carbo- and heterocycles using a tandem Mitsunobu reaction/3,3-sigmatropic rearrangement of allylic azide.[7] We

(1) (a) Gagneux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5956–5957. See also: (b) VanderWerf, C. A.; Heilser, R. Y.; McEwen, W. E. *J. Am. Chem. Soc.* **1954**, *76*, 1231–1235.

(2) (a) Murahashi, S.-I.; Tanigushi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292–3303. (b) Safi, M.; Fahrang, R.; Sinou, D. *Tetrahedron Lett.* **1990**, *31*, 527–530. (c) Arimoto, M.; Yamaguchi, H.; Fujita, E. *Tetrahedron Lett.* **1987**, *28*, 6289–6292.

(3) (a) Trost, B. M.; Pulley, S. R. *Tetrahedron Lett.* **1995**, *36*, 8737–8740. (b) Fava, C.; Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymm.* **2001**, *12*, 2731–2741. (c) Capaccio, C. A. I.; Varela, O. *Tetrahedron: Asymmetry* **2000**, *11*, 4945–4954. (d) Cardillo, G.; Fabbroni, S.; Gentillucci, L.; Perciaccante, R.; Piccinelli, F.; Tolornelli, A. *Org. Lett.* **2005**, *7*, 533–536. (e) Chida, N.; Tobe, T.; Murai, K.; Yamazaki, K.; Ogawa, S. *Heterocycles* **1994**, *38*, 2383–2388. (f) Magg, H.; Rydzewski, R. M. *J. Org. Chem.* **1992**, *57*, 5823–5831. (g) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1985**, *50*, 5005–5007.

(4) VanderWerf, C. A.; Heasley, V. L. *J. Org. Chem.* **1966**, *31*, 3534–3537.

(5) Panek, J. S.; Yang, M.; Muler, I. *J. Org. Chem.* **1992**, *57*, 4063–4064.

(6) Feldman, A. K.; Colasson, B.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 13444–13445.

(7) Gagnon, D.; Lauzon, S.; Godbout, C.; Spino, C. *Org. Lett.* **2005**, *7*, 4769–4771.

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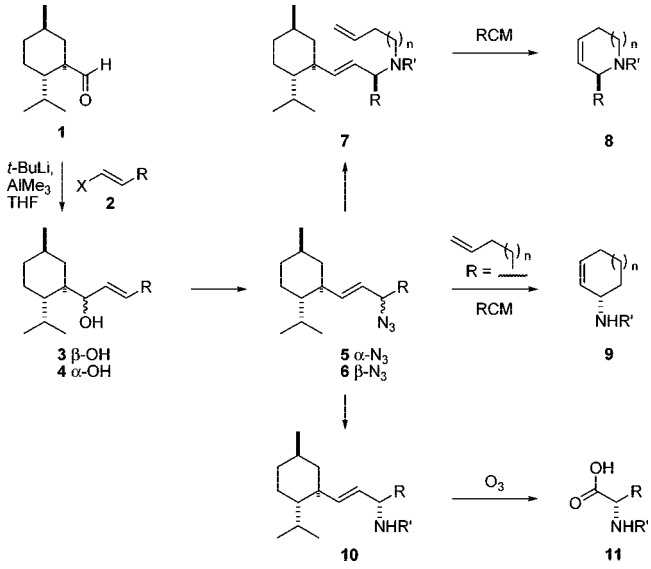
SCHEME 1. General Strategy for the Synthesis of Amino Acids, and Carbo- or Heterocycles



herein report a more complete investigation of this methodology as well as applications to the synthesis of natural alkaloids.

The general synthetic strategy is depicted in Scheme 1. The auxiliary *p*-menthane-3-carboxaldehyde (**1**) is easily available from menthone in two steps in either enantiomeric form.[8] The first two steps of the sequence are key steps that set up the stereochemistry of the nitrogen-bearing chiral carbon. Then, different methods of cleavage of the chiral auxiliary either lead to *N*-heterocycles **8**, carbocycles **9**, or amino acids **11**. Compounds **8** and **9** are particularly well suited for the synthesis of mono- or polycyclic alkaloids.

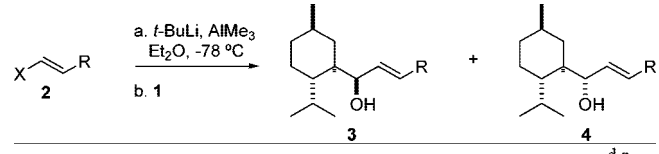
Results and Discussion

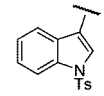
Synthesis of the Allylic Azides. The required vinyliodides **2** were prepared from the corresponding alkynes by hydrozirconation or hydroboration and a halogen quench. Metal−halogen exchange with common lithium bases generated the vinyllithium species corresponding to **2** that were added to *p*-menthane-3-carboxaldehyde (**1**) in the presence of $AlMe_3$ to give, stereoselectively, separable mixtures of diastereomeric alcohols **3** and **4** (Table 1, entries 1, 2, 4−10, and 12). The Felkin-Anh selectivity of the addition reaction decreases considerably in the absence of $AlMe_3$ (c.f. entries 1, 3 and 11).[9]

Submitting alcohols **3a**−**l** to the Mitsunobu reaction conditions in the presence of hydrazoic acid led to their stereoselective conversion to the allylic azides **5a**−**l** (Table 2). With the exception of azides **12j**, **12k**, and **12l** (entries 10, 11, and 12), all other azides were obtained as a single regioisomer **5** in good to excellent diastereomeric ratios. The diastereomeric ratio of the azide product **5** was generally higher when the size of the substituent R was larger (compare entries 2−3 with 4−5). The minor alcohols **4** were also submitted to the Mitsunobu/3,3-sigmatropic rearrangement reaction (Table 3, vide infra).

Two mechanistic pathways were initially considered to explain our results: an *anti* S_N2' displacement of the phosphonyloxy leaving group by the azide or a S_N2 displacement followed by a 3,3-sigmatropic rearrangement to the thermodynamically more stable regioisomer. Mitsunobu reactions on allylic alcohols rarely proceed by a S_N2' pathway, although some

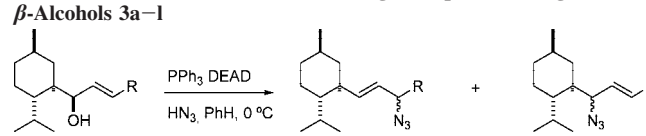
TABLE 1. $AlMe_3$-Promoted Vinyllithium Addition of Vinyllithium to 1

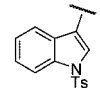


entry	2	X	R	Yield (%)[a]	d.r. (3 : 4)[b]
1	**2a**	**Br**	Me	77	6 : 1[c,d]
2	**2b**	**I**	*n*-Pr	54	99 : 1
3	**2c**	**I**	*n*-Bu	48	2 : 1[c]
4	**2d**	**I**	*t*-Bu	60	200 : 1
5	**2e**	**I**	Bn	64	170 : 1
6	**2f**	**Br**	$CH_2(C_6H_4)$(*o*-CH=CH_2)	67	46 : 1
7	**2g**	**I**	CH_2OTBS	57	19 : 1
8	**2h**	**I**	$(CH_2)_4OTBDPS$	56	35 : 1
9	**2i**	**I**	$(CH_2)_3CH(Me)OTBS$	56	49 : 1
10	**2j**	**I**	Ph	50	34 : 1
11	**2k**	---		71	3 : 1[e]
12	**2l**	**I**	Me_3Si	46	115 : 1

[a] Isolated yield of pure **3**. [b] Measured by HPLC with authentic mixtures of **3** and **4**. [c] Without $AlMe_3$. [d] ratio measured by ^1H NMR. [e] yield and ratio correspond to the addition of alkynyllithium to **1**: pure propargyl alcohol was then reduced to 3k with Red-Al in 77% yield.

TABLE 2. Tandem Mitsunobu/3,3-Sigmatropic Rearrangement of *β*-Alcohols 3a−l



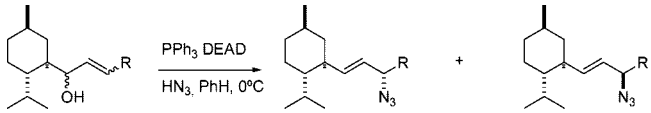
entry	3	R	Yield (%)[a]	d.r. (**5**:**6**)[b]	**5**:**12**
1	**3a**	Me	80	95 : 5	>98 : 2
2	**3b**	*n*-Pr	77	92 : 8	>98 : 2
3	**3c**	*n*-Bu	80	91 : 9	>98 : 2
4	**3d**	*t*-Bu	92	94 : 6	>98 : 2
5	**3e**	Bn	80	97 : 3	>98 : 2
6	**3f**	$CH_2(C_6H_4)$(*o*-CH=CH_2)	81	97 : 3	>98 : 2
7	**3g**	CH_2OTBS	76	>98 : 2	>98 : 2
8	**3h**	$(CH_2)_4OTBDPS$	98	>95 : 5[c]	>98 : 2
9	**3i**	$(CH_2)_3CH(Me)OTBS$	97	94 : 6[d]	>98 : 2
10	**3j**	Ph	78	3 : 1[e]	6 : 94
11	**3k**		98	4 : 1[e]	2 : >98
12	**3l**	Me_3Si	81	>98 : 2	1 : 1

[a] Isolated yield of **5** + **6**. [b] Measured by HPLC with authentic mixtures of **5** and **6**. [c] measured by NMR. [d] measured by NMR after reduction and conversion to the Mosher amide. [e] d.r. of **12**.

(8) Spino, C.; Godbout, C.; Beaulieu, C.; Harter, M.; Mwene-Mbeja, T. M.; Boisvert, L. *J. Am. Chem. Soc.* **2004**, *126*, 13312–13319.

(9) Spino, C.; Granger, M.-C.; Tremblay, M.-C. *Org. Lett.* **2002**, *4*, 4735–4737.

TABLE 3. Effect of Alcohol Stereochemistry and Double Bond Geometry on the Selectivity of the Mitsunobu Reactions of Alcohols 3 or 4



3 β-OH **4** α-OH **5** **6**

entry	3 or 4	R	alkene	Major product	Yield of 5 and 6 (%)[a]	5 : 6
1	**3a**	Me	*E*	**5a**	80	95 : 5[b]
2	**4a**	Me	*E*	**6a**	100	<10 : 90[b]
3	***Z*-3a**	Me	*Z*	**6a**	82	30 : 70[b]
4	***Z*-4a**	Me	*Z*	**5a**	89	66 : 34[b]
5	**4b**	*n*-Pr	*E*	**6b**	78	16 : 84[c]
6	**4d**	*t*-Bu	*E*	**6d**	76	16 : 84[c]
7	**4g**	CH_2OTBS	*E*	**6g**	60	10 : 90[c]
8	**4h**	$(CH_2)_4OTBDPS$	*E*	**6h**	76	<5 : 95
9	**4i**	$(CH_2)_3CH(Me)OTBS$	*E*	**6i**	76	12 : 88
10	**4j**	Ph	*E*	**6j**	78	1 : 3[d]
11	**4k**		*E*	**6k**	83	1 : 2[d]
12	**4l**	Me_3Si	*E*	**6l**	90	<2 : 98

cases involving electronically biased alkenes are known.[10] Large nucleophiles, such as imides, can also have a preference for S_N2' attack, and Mulzer and co-workers established that the substitution pattern on the allylic alcohol may influence the regioselectivity of Mitsunobu reactions involving phthalimide as nucleophile.[11] Since the phthalimide products cannot rearrange, the study provides a regioselectivity trend (S_N2 Vs S_N2') for such substrates and nucleophile. These authors suggested that steric effects and positive charge densities both influence the regiochemical outcome of the reaction. Predictably, the S_N2 reactions were completely stereospecific while the stereoselectivities of the S_N2' reactions ranged from 4:1 to 9:1. The stereochemistries of the major product from the S_N2' attack corresponded to an *anti* attack of the phthalimide on an $A^{1,3}$-strain minimized conformation.[12]

As a first mechanistic investigation into our particular system, we looked at what effect the stereochemistry of the carbinol carbon and the geometry of the double bond would have on the stereoselectivity of the reaction (Table 3). It is clear from the results that both are affecting considerably the stereoselectivity of the reaction (compare entries 1 vs 3 and 2 vs 4) but not its regiochemical outcome as only regioisomers **5** were observed in all cases studied. The *Z* geometry was particularly detrimental to the stereoselectivity of the reaction (entries 3 and 4). Also, the α-alcohols generally gave slightly lower stereoselectivities than their corresponding *β*-alcohols (compare entries 1, 2, 4, 7−12 in Table 2 with entries 1, 5, 6, 7−12 in Table 3, respectively). Conversely, the solvent seemed to have only a marginal effect overall: for compound **3a**, yields of azide **5a**

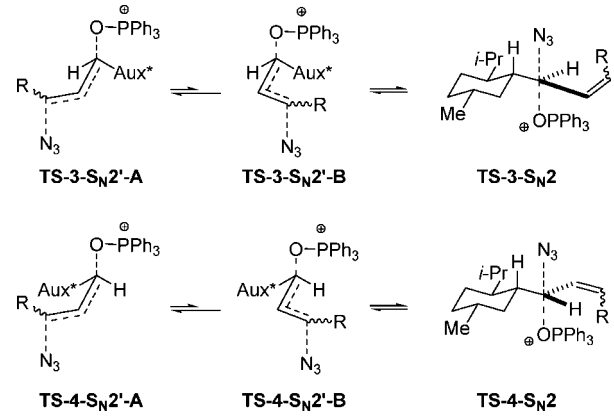


FIGURE 1. Proposed transition states for the S_N2 and S_N2' displacements of azide on the allylic phosphonyloxy intermediate from alcohols **3** and **4**.

varied from 73% in THF to 79% in benzene and 82% in dichloromethane while its %de was 87, 88, and 82% respectively.

We can safely conclude from these results that the reaction does not involve an allylic carbocation. Indeed, alcohols **3** and **4** would then lead to identical carbocations and should thus have given indentical ratios of azides **5** and **6**. In addition, it would be surprising if the stereoselectivity of a purported S_N2' pathway would be so sensitive to alkene geometry or carbinol stereochemistry (Figure 1). Rather, we think that the stereoselectivity depends on a competition between the S_N2 and S_N2' pathways, the former being stereospecific, the latter being poorly stereoselective. The displacement is followed by a stereospecific rearrangement that favors isomer **5** because of steric repulsion between the azide and the bulky menthyl nucleus. The alkene geometry and the carbinol stereochemistry could influence the amount of S_N2 vs S_N2' attack by the azide ion: for example, a small change in conformation around the carbinol methine could raise or lower the energy of the S_N2 transition state while the energy of the S_N2' transitions state would likely remain the same (Figure 1).

On the other hand, S_N2' displacements are thought to occur principally *syn* to the leaving group, especially with small nucleophiles like an azide ion.[12] In our case, all stereoselectivities were in favor of the "*anti*" displacement product. Thus, we have carried out a series of reactions varying the phosphine for its electronic and steric size (Table 4): if indeed a S_N2' displacement were the prevalent pathway, we would expect to see variations in the stereoselectivity of the reaction. Electron-deficient phosphines gave better yields of products, tris(pentafluorophenyl)phospine being an exception (entry 9), but more importantly, the regioselectivity was again complete for the *γ*-product **5d**. In addition, the diastereoselectivity seemed independent of the size of the phosphine group. In fact, many bulkier phosphines gave a slightly lower ratio of diastereomers (entries 2, 10, and 11). Such results are difficult to reconcile with a direct S_N2' displacement of the leaving group.

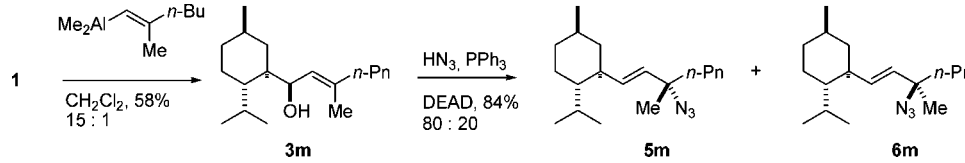
Now, lets consider the fact that alcohols **3j−k** led to mixtures of regioisomers **5j−k** and **12j−k**, favoring the latter, probably because conjugation renders isomer **12** more stable (Table 2, entries 10 and 11). Moreover, the reactions of **3j** and **3k** were less stereoselective than the other ones. Yet, their diastereomers **4j** and **4k** underwent the same reaction to give the opposite mixture of diastereomers **13j**:**12j** (and **13k**:**12k**) in similar yields and ratios (Table 3, entries 10 and 11). Also, alcohol **3l**, having a silyl group on the alkene, led to a 1:1 mixture of regioisomers

(10) (a) Charrette, A. B.; Côté, B.; Monroc, S.; Prescott, S. *J. Org. Chem.* **1995**, *60*, 6888–6894. (b) Sobti, A.; Sulikowski, G. A. *Tetrahedron Lett.* **1994**, *35*, 3661–3664. (c) Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron* **1995**, *51*, 255–272.

(11) Mulzer, J.; Funk, G. *Synthesis* **1995**, 101–112.

(12) (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901–1904. (b) Stohrer, W.-D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 613–614.

SCHEME 2. Tandem Mitsunobu/3,3-Sigmatropic Rearrangement of Alcohol 3m



SCHEME 3. Mitsunobu Reaction of Dienol 3n

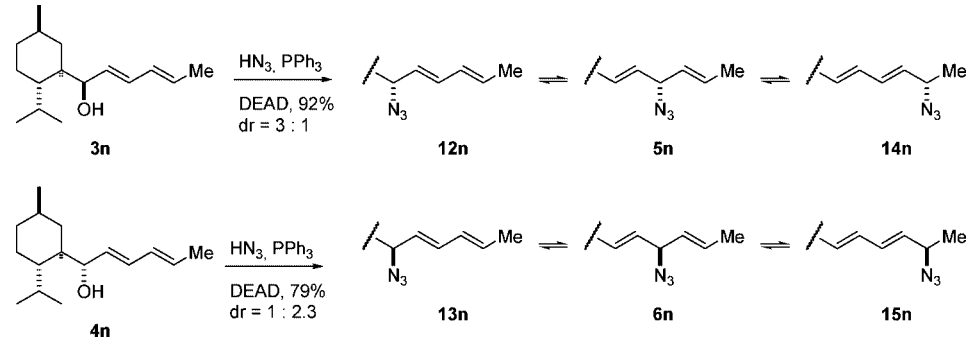
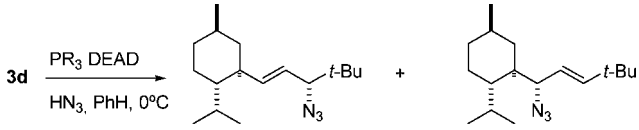


TABLE 4. Tandem Mitsunobu/3,3-Sigmatropic Rearrangement of Alcohols 3d with Different Phosphines



entry	PR_3	yield (%)	5d/6d[a]	5d/12d
1	Ph_3P	94	94:6	<99:1
2	$(o\text{-Tol})_3P$	15	91:9	<99:1
3	Cy_3P	0	—	—
	$(p\text{-MeO-Ph})_3P$	0	—	—
4	$(p\text{-Cl-Ph})_3P$	85	92:8	<99:1
5	$(EtO)_3P$	0	—	—
6	$(thp)_3P$	50	92:8	<99:1
7	$(pyr)Ph_2P$	92	92:8	<99:1
8	$(m\text{-Cl-Ph})_3P$	90	92:8	<99:1
9	$(C_6F_5)_3P$	0	—	—
10	DPPA	50	91:9	<99:1
11	$(Napht)Ph_2P$	99	91:9	<99:1

[a] Measured by GC (pure **6d** was prepared separately starting from **4d**).

5l and **12l** but, this time, each isomer was diastereomerically pure (Table 2, entry 12). Similarly, starting with diastereomeric alcohol **4l**, diastereomerically pure **6l** and **13l** were obtained as a 1:1 mixture. Lastly, trisubstituted allylic alcohol **3m** was treated under the same reaction conditions to afford a single regioisomers **5m** with a modest 4:1 ratio of diastereomers (Scheme 2).

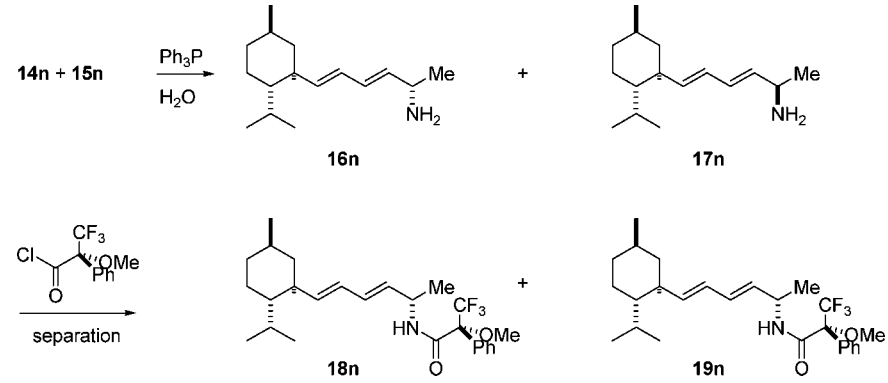
Mechanistic studies by Padwa and co-workers on the 3,3-sigmatropic rearrangement of some allylic azides led them to believe that the reaction is a concerted one and likely does not involve ion pairs.[13] This is certainly the case here as regioisomers **5** would likely be isolated as mixtures of diastereomers were ionic intermediates involved, unless tight ion pairs were involved with no time for bond rotation (Figure 2, ion pair **I**). A stereoselective rearrangement following a stereospecific S_N2 displacement of the azide ion, on the other hand, would account for the overall stereoselectivity of the reaction. The double bond geometry effectively keeps the stereochemical integrity of the allylic azide intact despite a fast equilibrium between the two regioisomers even at room temperature (Figure 2, **II** and **III**) because allylic azides ***Z*-5** possessing a *Z* double bond were never observed.

The above results are thus best explained in the following way: displacement of the phosphonyloxy group by the azide ion takes place mainly by way of the S_N2 mechanism. That part is stereospecific. Then a concerted 3,3-sigmatropic rearrangement generates azides **5**, stereoselectively. However, as the positive charge density becomes higher on the distal alkene carbon of the alcohols **3**, an increased amount of displacement by the azide ion occurs via the S_N2' mechanism, which is poorly stereoselective. Thus, aryl-substituted allylic alcohols **3j** and **3k** as well as trisubstituted allylic alcohol **3m** give rise to more S_N2' displacement then the alkyl monosubstituted allylic alcohols **3a**−**i**. That causes the poorer stereoselectivity observed in the reactions of **3j**,**k**,**m**. This is certainly in line with the findings of Mulzer and Funk on the Mitsunobu of imides.[11] The silyl-substituted allylic alcohol **3l** probably undergoes solely a S_N2 displacement because of the steric effect of the bulky silyl group and a decreased positive charge at the distal alkene carbon (the one bearing the silyl group). The size (and perhaps the electronics) of the silyl group leads to an equal mixture of regioisomers **5l** and **12l**, each diastereomerically pure because the rearrangement is concerted.

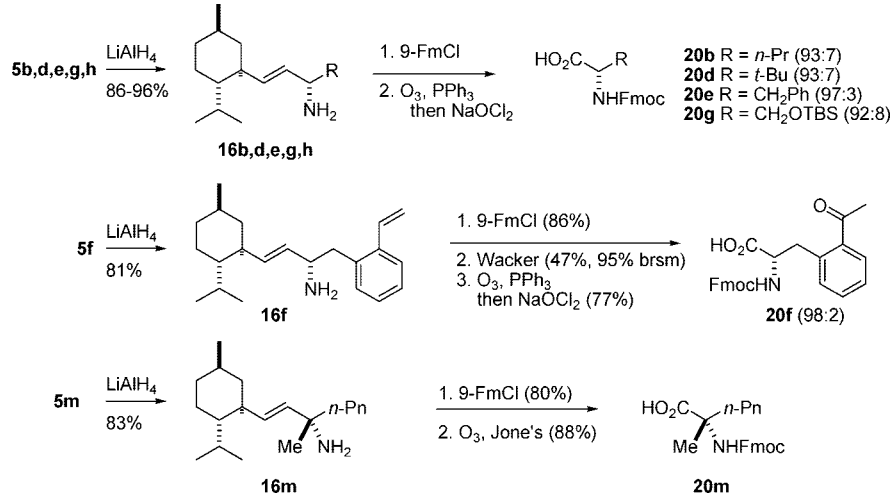
Interestingly, we submitted dienol **3n** to the Mitsunobu reaction conditions and observed the formation of azide **14n** exclusively, isolated as a 3:1 mixture of diastereomers (Scheme 3). The major diastereomer was unambiguously identified as **14n** by reduction to the mixture of amines **16n/17n** and their conversion to the separable Mosher esters **18n** and **19n** (Scheme 4). Compound **18n** crystallized and a X-ray diffraction analysis on a single crystal confirmed the structure. It is likely that the S_N2 pathway is again the major one and that neither regioisomer **12n** nor **5n** is thermodynamically favored, the former because of steric reasons, the latter because the diene is not conjugated. Stereoisomeric alcohol **4n** gave the corresponding azide **15n** as a 1:2.3 mixture of diastereomers (Scheme 3). Conversion to the separable

(13) Padwa, A.; Sa, M. M. *Tetrahedron Lett.* **1997**, *38*, 5087–5090.

SCHEME 4. Proof of Stereochemistry of Azide 14n and 15n



SCHEME 5. Synthesis of Non-Racemic α-Amino-Acids 20



Mosher esters **19n** and **18n** confirmed that **15n** was the major compound. The low observed diastereomeric ratios indicate that the vinylic substituent, like the phenyl substituent in **3j**, favors an increased amount of S_N2' displacement probably because of an increase in positive charge density at that carbon. There could have been some attack at the carbon δ to the alcohol as well.

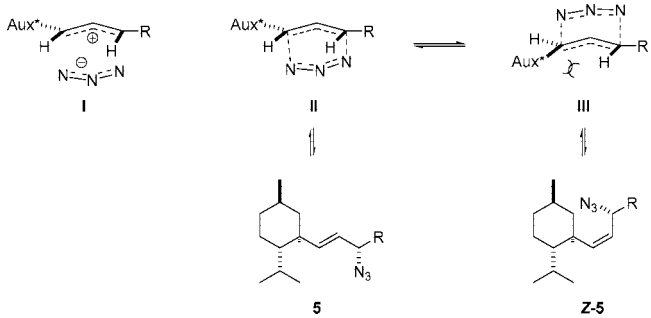


FIGURE 2. Mechanism and stereospecificity of the 3,3-sigmatropic rearrangement.

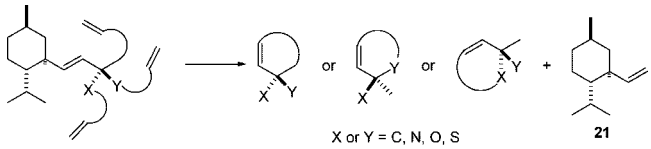


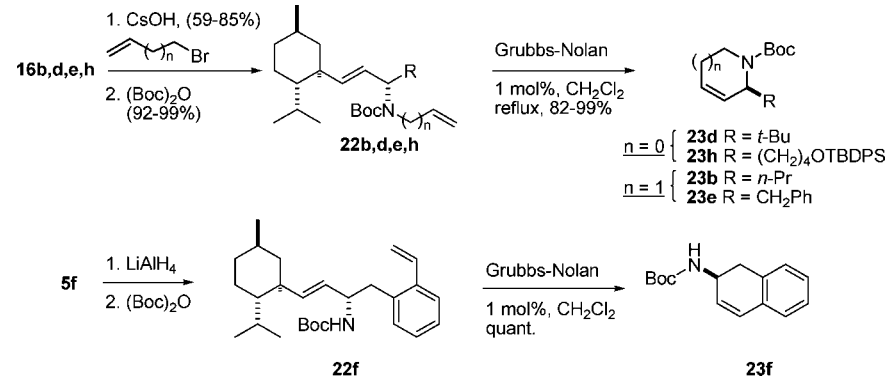
FIGURE 3. Carbo- and heterocycles from RCM cleavage of the chiral auxiliary.

Thus, only groups capable of stabilizing the double bond, by conjugation or otherwise, will disrupt the perfect thermodynamic regioselectivity for this reaction. Notably, even the bulky *t*-butyl group does not appreciably destabilize the desired regioisomer **5d**. To the best of our knowledge, this is the first chiral auxiliary system capable of biasing to such a degree the thermodynamic equilibrium of allylic azides. Regioisomers **5** are quite useful compounds that can lead to amino acids or *N*-heterocycles depending on how we cleave the auxiliary, that is to say by oxidative cleavage or by RCM (vide infra), respectively.

Synthesis of Amino Acids. Reduction of azides **5b**,**d**,**e**,**g** procured the corresponding amines **16b**,**d**,**e**,**g** with no trace of undesired regioisomers (similarly, the corresponding azides **6b**,**d**,**e**,**g** were converted to amines **17b**,**d**,**e**,**g**). This is perhaps a reflection of the very low concentration of azides **12** (or **13**) and/or of the higher reactivity of azides **5** (or **6**). We have then made a number of Fmoc-protected α-amino acids **20** by protection of the amine and ozonolysis of the double bond (Scheme 5). The measured enantiomeric excesses of the amino acids matched the diastereomeric excesses of the corresponding azide.

Synthesis of N-Heterocycles. Perhaps one of the most interesting feature of our chiral auxiliary system is its capability to undergo RCM cleavage to give directly carbo- or heterocyclic compounds and the chiral auxiliary in a recoverable form (Figure 3).[14] The latter (compound **21**) is highly volatile and very easy to remove from the mixture and recover. It can be transformed

SCHEME 6. RCM Cleavage of the Auxiliary on *N*-Boc Derivatives 22



back to **1** by ozonolysis. Because the chain bearing the alkene for the RCM cleavage can be at one of three places, one can prepare a number of interesting structures (Figure 3).

Schemes 6 and 7 depict examples of RCM cleavages of certain derivatives of some of the azides listed in Table 2. The RCM reactions are divided in two categories: those that were carried out on protected amines **22** (Scheme 6) and those that were carried out on amides **24**, **25**, or **27** (Scheme 7). The first category requires very mild conditions using 1 mol% of the Grubbs-Nolan catalyst or Grubbs' first generation catalyst, in refluxing dichloromethane. Protection of the amine is necessary otherwise no reaction takes place. Recovery of the auxiliary **21** was not done systematically but it was isolated several times in excess of 80% yield.

The amides **24**, **25**, and **27** required higher catalyst loading at 5 mol% but proceeded well at the refluxing temperature of dichloromethane. Normally, α,β-unsaturated carbonyls are not good alkenes with which to initiate the RCM.[15,16] That is why we first performed the RCM via the relay RCM strategy starting with amide **24o** (Scheme 7).[17] In 10 min, the reaction was complete and gave 85% yield of pyrrolidone **26o**. Surprisingly, the RCM was slower but just as efficient when carried out directly from amide **25o**. In this case, the RCM must be initiated at the α,β-unsaturated amide since initiation at the internal double bond is not possible.[15b]

RCM cleavage of amides **27c** and **27h** required the use of an external Lewis acid.[18] The cause of failure when there is no Lewis acid is the strong coordination of the amide oxygen to the ruthenium carbene intermediate.[16] We surveyed several Lewis acids but $PhBCl_2$ gave the best results.

Synthesis of Natural Alkaloids. N-Heterocycles have a huge potential as therapeutic agents and they are valuable synthetic intermediates to natural alkaloids that possess large spectra of biological activities.[19] To demonstrate the usefulness of our overall strategy, we carried out the synthesis of some simple alkaloids (Figure 4).

Double bond reduction in **23b** gave the known *N*-protected alkaloid (+)-coniine **32** for a total of eight steps and 19% yield starting from 1-pentyne (Scheme 8).[20] Coniine is often used as prototypical target for piperidine synthesis and due to its high volatility, it is either converted to its *N*-Boc derivative or isolated as it hydrochloride salt.[18] It is a major toxic principle of poison hemlock (*Conium maculatum*) and was apparently the first alkaloid ever synthesized by Ladenburg in 1886.[21]

Lentiginosine is part of a small family of polyhydroxylated indolizidine alkaloids, some of which are potent antiviral agents.[22] Lentiginosine was isolated from *Astralagus lentiginosus* and its structure was elucidated in 1990 by Elbein and co-workers.[20b] However, its absolute configuration was revised after Brandi and co-workers achieved the total synthesis of (+)- and (−)-lentiginosine.[23] It was found to be a reasonably good inhibitor of fungal α-glucosidase, amyloglucosidase ($K_i = 1 \times 10^{-5}$ M), but not of other α-glucosidases. It has been synthesized by Isobe and his team using a rearrangement of cyanates to isocyanates.[24] We prepared (+)-lengitinosine from **23h** by stereoselective epoxidation of the alkene,[25] cyclization, and regioselective opening of the epoxyde (Scheme 9). Starting from

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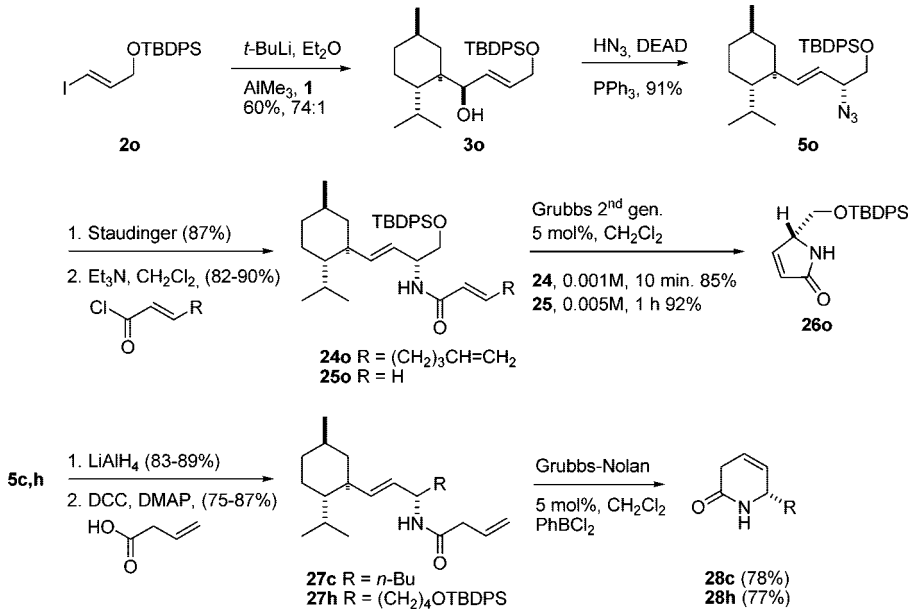
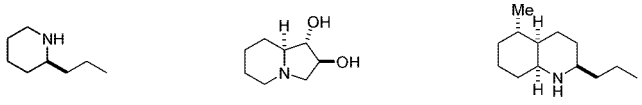
SCHEME 7. RCM of Amides 24a, 25o, 27c, and 27h



5-hexynol, the synthesis of (+)-lentiginosine was achieved in 13 steps in 7% overall yield for an average of 82% yield per step.



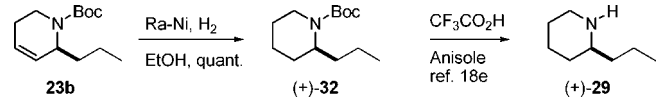
(+)-coniine (**29**) (+)-lentiginosine (**30**) (+)-pumiliotoxin C (**31**)

FIGURE 4. Alkaloids synthesized.

South American poison dart frogs secrete toxic alkaloids in their skin. Pumiliotoxin C was the first member to be isolated from *Dendrobates pumilio*, also called the strawberry poison frog in Costa Rica.[26] Frogs held in captivity do not secrete alkaloids. *Scheloribatid* mites have been identified as an important source of pumiliotoxins for the frogs.[27] The structure of pumiliotoxin C was revealed by synthesis and X-ray analysis in 1975[28] but the absoluted configuration of natural (−)-pumiliotoxin C was confirmed as that shown in Scheme 10 after Oppolzer and co-workers completed the synthesis of both enantiomers.[29]

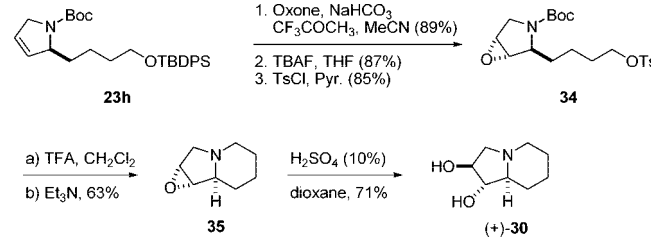
Iodide **2i** was prepared in four steps from racemic 2-methylfuran (Scheme 10). Tables 1 and 2 indicate the yields and selectivities of its converstion to azide **5i**. Then, reduction of azide **5i** with $LiAlH_4$ followed by acylation of the resulting amine afforded amide **27i**. RCM in refluxing dichloromethane in the presence of dichlorophenylborane was efficient and led directly to the *N*-heterocycle. It was found that an aqueous workup of this reaction caused partial deprotection of the alcohol, probably from hydrochloric acid generated by the reaction of water and the dichloroborane. Indeed, it was possible

SCHEME 8. Synthesis of (+)-*N*-Boc-coniine (+)-32



23b (+)-**32** (+)-**29**

SCHEME 9. Synthesis of (+)-Lentiginosine 30



23h **34** **35** (+)-**30**

to optimize this procedure to obtain directly **28i** in quantitative yield using an acidic workup. Conversion of the alcohol to iodide **38** went uneventfully. Radical cyclization formed the second ring of pumiliotoxin C stereoselectively (**39**) in modest yield. We tried a vast number of variations on this cyclization, including replacing the iodide by bromide, thiocarbonate, or xanthate, changing the solvents, temperature, radical initiation procedures, using hydridre free conditions and atom transfert techniques, but we were unable to augment the yield of **39**.[30] Zard pointed out that 6-exotrig cyclizations to give decaline-type systems are particularly difficult.[31] In our particular case, facile hydrogen abstraction compounds the problem and leads to reduced (**40**) or aromatized products (**41**) as well as dimerization products (**42** and **43**) (Figure 5). Nonetheless, the radical cyclization created two chiral centers stereoselectively via transition state **38A**. The synthesis was completed by imino ether formation, Grignard addition and reduction of the unstable imine in good yield for the three steps.[32] Overall, the synthesis was carried out in 15 steps from 2-methylfuran with an overall

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SCHEME 10. Synthesis of (+)-Pumiliotoxin C 31

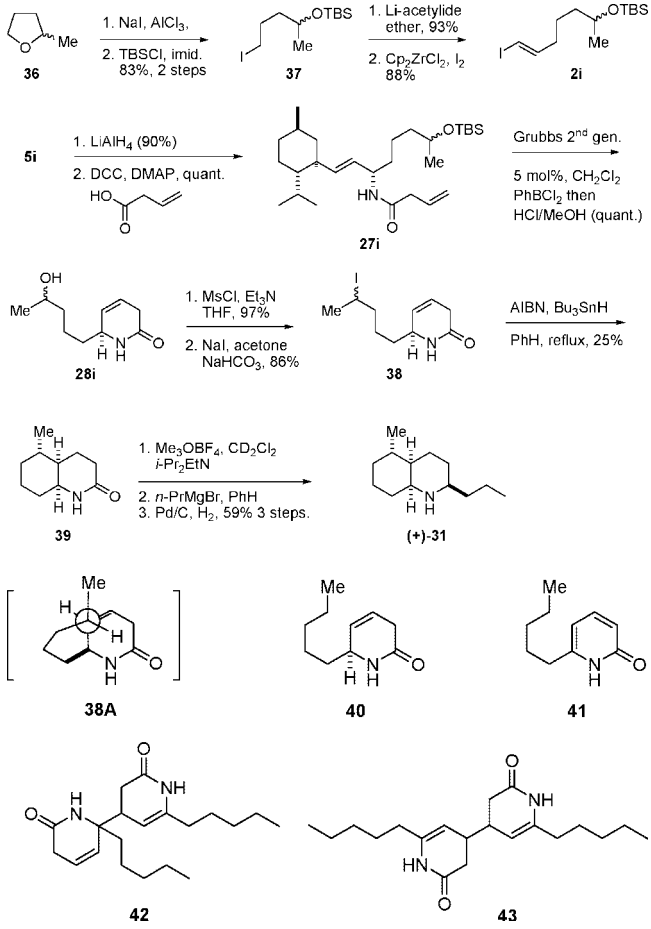

FIGURE 5. Transitions state and byproduct of the radical cyclization of **36**.

yield of 4% and an average yield of 81% per step. So despite the modest yield of the radical cyclization, the overall synthesis is short and efficient.

In conclusion, an unusual tandem Mitsunobu/3,3-sigmatropic rearrangement of allylic azides combined with RCM cleavage of our chiral auxiliary allows for synthesis nonracemic of *N*-heterocycles. The role of the chiral auxiliary is to induce stereochemistry but also to sterically bias the equilibrium mixture of the allylic azides. Chiral quaternary azides are also available by this method, albeit in lower diastereomeric excess. We have successfully applied the strategy to the synthesis of amino acids and natural alkaloids. The synthesis of complex alkaloids are underway and will be presented in due course.

Experimental Section

6-*t*-Butyldiphenylsilyloxy-1-iodo-1-hexene 2 h. In a 500 mL r.b. flask was dissolved 1-*t*-butyldiphenylsilyloxy-5-hexyne (10.00 g, 29.71 mmol) in anhydrous CH_2Cl_2 (100 mL). The solution was cooled to 0 °C, and a solution of $Br_2BH \cdot SMe_2$ 1.0 M in CH_2Cl_2 (35.7 mL, 35.66 mmol) was added dropwise over a period of 10 min. The reaction mixture was was stirred at RT overnight (18 h), and a solution of NaOH 3.0 M (49.5 mL, 148.57 mmol) was added dropwise after cooling to 0 °C. A white solid was precipated. This slurry was then stirred at RT for 3 h and then cooled again to 0 °C. Iodine (11.30 g, 44.57 mmol) was added in small portions. The resulting reaction mixture was stirred for 2 h at RT. Then, the aqueous phase was extracted with 3 portions of Et_2O and the combined organic extracts were washed with 1 portion of saturated solution of $Na_2S_2O_3$, one portion of water, and once with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a colorless oil. The crude product was purified on silica gel with 5:95/EtOAc:Hexanes as eluant to afford iodide **2h** as a colorless oil (10.67 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.67−7.64 (dd, 4H, J = 7.7 Hz, 1.7 Hz), 7.43−7.35 (m, 6H), 6.53−6.44 (m, 1H), 5.94 (d, 1H, J = 14.3 Hz), 3.64 (t, 2H, J = 5.8 Hz), 2.03 (q, 2H, J = 5.1 Hz), 1.59−1.41 (m, 4H), 1.05 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 146.5 (d), 135.7 (d), 134.1 (s), 139.7 (d), 127.9 (d), 74.9 (s), 63.6 (t), 35.9 (t), 31.9 (t), 27.1 (q), 24.8 (t), 19.4 (s). IR (film) • (cm^{-1}): 3070, 3049, 2931, 2858, 1472, 1427, 1111, 943. LRMS (*m*/*z*, relative intensity): 407 [M − C_4H_9]$^+$, 64), 309 (100), 249 (20), 199 (44), 181 (19), 81 (27). HRMS calcd for $C_{18}H_{20}IOSi$: 407.0328, found 407.0325.

(E)-5-*t*-Butyldimethylsiloxy-1-iodo-1-heptene 2i. 2-Methyltetrahydrofuran **36** (20 mL, 200 mmol) was added to a solution of aluminum chloride (150 g, 1.00 mol) and sodium iodide (133 g, 1.00 mol) in acetonitrile (220 mL) at 0 °C. The mixture was stirred 2 h at 0 °C, and a 1 N HCl aqueous solution was added until complete dissolution of salts. The aqueous layer was extracted with pentane (3 × 300 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The iodoalcohol (41.6 g, 97%) was obtained as a colorless oil and used without further purification.

Imidazole (33.0 g, 485 mmol) and *t*-butylchlorodimethylsilane (32.0 g, 212 mmol) were added to the iodoalcohol (41.6 g, 194 mmol) in dichloromethane (800 mL) at RT. The mixure was stirred at RT for 16 h and then quenched with water (500 mL). The aqueous layer was extracted with dichloromethane (3 × 400 mL) and the combined organic layers were washed once with brine, dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (from 0 to 2% diethyl ether in hexanes) to yield pure iodide **37** (50.3 g, 83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.82 (sext, 1H, J = 6.0 Hz), 3.19 (t, 2H, J = 7.2 Hz), 1.98−1.75 (m, 2H), 1.54−1.46 (m, 2H), 1.13 (d, 3H, J = 6.0 Hz), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). IR (neat) • (cm^{-1}) 2955, 2927, 2885, 2856, 1465, 1317, 1248, 1129, 1082, 832, 770. LRMS (*m*/*z*, relative intensity) 313 ([M$^+$ − CH_3], 2), 271 ([M$^+$ − C_4H_9], 45), 229 (100). HRMS calcd for $C_7H_{16}IOSi$ [M$^+$ − C_4H_9]: 271.0015, found: 271.0006.

A solution of the iodide **37** (46.4 g, 141 mmol) in diethyl ether (700 mL) was slowly added to lithium acetylide complexed with ethylene diamine (85%, 31.1 g, 289 mmol) in a pentane:DMSO solvent system (5:2, 1.23 L) at 0 °C. The mixture was stirred, allowed to slowly warm up to RT for 16 h, and then quenched with a half-saturated NH_4Cl aqueous solution (1.0 L). The aqueous layer was extracted with diethyl ether (3 × 800 mL), and the combined organic layers were washed once with water, once with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (from 0 to 5% ethyl ether in hexanes) to yield pure alkyne (29.6 g, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.81 (sext, 1H, J = 6.0 Hz), 2.19 (td, 2H, J = 5.9, 2.5 Hz), 1.94 (t, 1H, J = 2.5 Hz), 1.66−1.46 (m, 4H), 1.13 (d, 3H, J = 6.0 Hz), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 84.3 (s), 68.2 (d), 68.0 (d), 38.6 (t), 25.8 (q), 24.7 (t), 23.8 (q), 18.4 (t), 18.0 (s), −4.5 (q), −4.8 (q). IR (neat) • (cm^{-1}) 3317, 2957, 2935, 2858, 2120, 1471, 1377, 1255, 1138, 1093, 1030, 837, 778. LRMS (*m*/*z*, relative intensity) 211 ([M$^+$ − CH_3], 2), 169 ([M$^+$ − C_4H_9], 5), 75 (100). HRMS calcd for $C_{12}H_{23}OSi$ [M$^+$ − CH_3]: 211.1518, found: 211.1514.

Shielded from light, a solution of lithium triethylborohydride in THF (1.0 M, 33.1 mL, 33.1 mmol) was added dropwise to bis-(cyclopentadienyl)zirconium chloride (9.68 g, 33.1 mmol) in THF (190 mL) at 0 °C. The mixture was stirred 1 h at RT before a solution of the 5-*t*-butyldimethylsiloxy-1-heptyne (5.00 g, 22.1

mmol) in THF (30 mL) was added. The mixture was stirred 2 h at room temprature, cooled down to 0 °C. and iodine (9.30 g, 36.6 mmol) was added in three portions. The mixture was stirred and allowed to slowly warm up to RT for 16 h. The resulting red solution was quenched with a saturated $NaHCO_3$ aqueous solution (150 mL) until the solution became yellow. The aqueous layer was extracted with diethyl ether (3 × 150 mL). and the combined organic layers were washed once with a saturated $Na_2S_2O_3$ aqueous solution, dried over anhydrous $MgSO_4$. and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (from 0 to 1% diethyl ether in hexanes) to yield pure vinyliodide **2i** (6.1 g, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.50 (dt, 1H, J = 14.3, 7.0 Hz), 5.97 (d, 1H, J = 14.3 Hz), 3.77 (sext, 1H, J = 6.0 Hz), 2.05 (q, 2H, J = 7.0 Hz), 1.52−1.31 (m, 4H), 1.11 (d, 3H, J = 6.0 Hz), 0.88 (s, 9H), 0.04 (s, 6H). IR (neat) • (cm^{-1}) 2953, 2930, 2856, 1464, 1372, 1252, 1137, 1095, 1031, 833, 768. LRMS (*m*/*z*, relative intensity) 339 ([M$^+$ − CH_3], 1), 297 ([M$^+$ − C_4H_9], 65), 75 (100). HRMS calcd for $C_9H_{18}IOSi$ [M$^+$ − C_4H_9]: 297.0172, found: 297.0180.

Allylic Alcohol 3h. Prepared according to the general procedure for allylic alcohols **3** starting with vinyliodide **2h** (10.60 g, 22.84 mmol) and *p*-menthyl-3-carboxaldehyde **1** (3.2 g, 19.03 mmol) to give allylic alcohol **3h** as a colorless oil (4.31 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.66 (dd, 4H, J = 7.7 Hz, 1.7 Hz), 7.45−7.34 (m, 6H), 5.65−5.47 (m, 2H), 4.37 (d, 1H, J = 4.4 Hz), 3.67 (t, 2H, J = 6.1 Hz), 2.13 (dquint, 1H, J = 6.6 Hz, 2.2 Hz), 2.04 (q, 2H, J = 6.8 Hz), 1.72−1.46 (m, 9H), 1.44−1.24 (m, 3H), 1.04 (s, 9H), 1.05−0.79 (m, 2H), 0.93 (d, 3H, J = 7.2 Hz), 0.87 (d, 3H, J = 6.6 Hz), 0.76 (d, 3H, J = 7.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 135.6 (d), 134.1 (s), 132.6 (d), 130.4 (d), 129.5 (d), 127.6 (d), 71.3 (d), 63.7 (t), 44.8 (d), 43.0 (d), 35.2 (t), 33.9 (t), 32.8 (d), 32.1 (t), 26.9 (q), 26.3 (d), 25.6 (t), 24.3 (t), 22.9 (q), 21.6 (q), 19.2 (s), 15.5 (q). IR (film) • (cm^{-1}): 3447, 3069, 2956, 2931, 2859, 1472, 1428, 1111, 973. LRMS (*m*/*z*, relative intensity): 449 ([M − C_4H_9]$^+$, 10), 293 (14), 233 (21), 199 (100), 177 (22), 137 (49), 109 (29), 95 (64), 81 (39). HRMS calcd for $C_{29}H_{41}O_2Si$: 449.2876, found 449.2870. $[\alpha]^{20}_D$ = −7.7 (*c* 2.57, $CHCl_3$).

Allylic Alcohol 3i. Prepared according to the general procedure for allylic alcohols **3** starting with vinyliodide **2i** (320 mg, 0.90 mmol) in diethyl ether (3 mL) at −78 °C, (−)-*p*-menthane-3-carboxaldehyde **1** (130 mg, 0.77 mmol) to yield pure alcohol **3i** (173 mg, 56%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.59 (dt, 1H, J = 15.4, 6.3 Hz), 5.50 (dd, 1H, J = 15.4, 4.7 Hz), 4.34 (d, 1H, J = 4.7 Hz), 3.76 (sext, 1H, J = 6.0 Hz), 2.12 (septd, 1H, J = 7.0, 1.8 Hz), 2.02 (q, 2H, J = 6.3 Hz), 1.69−1.60 (m, 3H), 1.49−1.21 (m, 9H), 1.09 (d, 3H, J = 6.0 Hz), 0.99−0.78 (m, 5H), 0.90 (d, 3H, J = 7.0 Hz), 0.86 (s, 9H), 0.74 (d, 3H, 7.0 Hz), 0.02 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 132.4 (d), 130.4 (d), 71.2 (d), 68.4 (d), 44.7 (d), 42.9 (d), 39.2 (t), 35.1 (t), 33.8 (t), 32.7 (d), 32.2 (t), 26.2 (d), 25.9 (q), 25.4 (t), 24.2 (t), 23.9 (q), 22.8 (q), 21.5 (q), 18.1 (s), 15.4 (q), −4.4 (q), −4.8 (q). IR (neat) • (cm^{-1}) 3385 (large), 2957, 2929, 2864, 1466, 1378, 1257, 838, 777. LRMS (*m*/*z*, relative intensity) 339 ([M$^+$ − C_4H_9], 5), 74 (100). HRMS calcd for $C_{20}H_{39}O_2Si$ [M$^+$ − C_4H_9]: 339.2719, found: 339.2723. $[\alpha]^{20}_D$ = −7.9 (*c* = 2.06, $CHCl_3$).

Allylic Azide 5h. Prepared according to the general procedure for allylic azides **5** starting with allylic alcohol **3h** (1.50 g, 2.960 mmol) and triphenylphosphine (1.55 g, 5.919 mmol) in benzene (30.0 mL), hydrazoic acid (4.2 mL, 1.4 M in benzene, 5.92 mmol), and diethylazodicarboxylate (DEAD) (1.030 g, 5.919 mmol) to afford azide **5h** as a colorless oil (1.55 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.66 (dd, 4H, J = 7.7 Hz, 1.7 Hz), 7.45−7.34 (m, 6H), 5.51−5.43 (m, 1H), 5.36−5.27 (m,1H), 3.76 (q, 1H, J = 7.1 Hz), 3.64 (t, 2H, J = 6.3 Hz), 1.96−1.85 (m, 2H), 1.75−1.70 (m, 1H), 1.65−1.25 (m, 10H), 1.04 (s, 9H), 1.05−0.83 (m, 3H), 0.86 (d, 3H, J = 7.1 Hz), 0.85 (d, 3H, J = 6.6 Hz), 0.71 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 140.2 (d), 135.5 (d), 133.9 (s), 129.5 (d), 127.5 (d), 126.9 (d), 65.0 (d), 63.5 (t), 46.7 (d), 44.7 (d), 43.1 (t), 35.1 (t), 34.4 (t), 32.4 (d), 32.1 (t), 31.6 (t), 28.0 (d), 26.9 (q), 23.8 (t), 22.5 (q), 22.3 (t), 21.4 (q), 19.2 (s), 15.1 (q), 14.1 (q). IR (film) • (cm^{-1}): 3072, 3049, 2962, 2868, 2095, 1471, 1428, 1237, 1111, 973. LRMS (*m*/*z*, relative intensity): 549 ([M − NH_4]$^+$, 12), 508 (15), 274(45), 248 (30), 182 (50), 112 (99), 98 (100), 78 (93). HRMS calcd for $C_{33}H_{53}N_4OSi$: 549.3988, found 549.3984 (for [MNH_4]). $[\alpha]^{20}_D$ = −25.1 (*c* 3.67, $CHCl_3$).

Allylic Azide 5i. Prepared according to the general procedure for allylic azides **5** starting with allylic alcohol **3i** (4.06 g, 10.2 mmol, diethyl azodicarboxylate (3.2 mL, 20.4 mmol), hydrazoic acid solution in benzene (1.44 M, 14.2 mL, 20.4 mmol), and triphenylphosphine (5.37 g, 20.5 mmol) in benzene (50 mL) to yield pure azide **5i** (4.16 g, 97%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.48 (dd, 1H, J = 15.2, 9.1 Hz), 5.32 (dd, 1H, J = 15.2, 8.2 Hz), 3.82−3.72 (m, 2H), 2.00−1.87 (m, 2H), 1.75−1.71 (m, 1H), 1.65−1.55 (m, 2H), 1.51−1.26 (m, 7H), 1.11 (d, 3H, J = 6.0 Hz), 1.03−0.67 (m, 10H), 0.88 (s, 9H), 0.71 (d, 3H J = 6.6 Hz), 0.04 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 140.3 (d), 126.9 (d), 68.4 (d), 65.0 (d), 46.7 (d), 44.7 (d), 43.2 (t), 39.3 (t), 39.2 (t), 35.1 (t), 34.8 (t), 32.4 (d), 28.0 (d), 25.9 (q), 23.8 (q), 22.5 (q), 22.2 (t), 21.4 (q), 18.1 (s), 15.1 (q), −4.4 (q), −4.8 (q). IR (neat) • (cm^{-1}) 2958, 2934, 2859, 2098, 1468, 1374, 1251, 1054, 979, 843. LRMS (*m*/*z*, relative intensity) 393 ([M$^+$ − N_2], 5), 378 (M$^+$ − CH_3N_2, 10), 364 (M$^+$-C_4H_9, 5), 74 (100). HRMS calcd for $C_{20}H_{38}N_3OSi$ [M$^+$ − C_4H_9]: 364.2784, found: 364.2786. $[\alpha]^{20}_D$ = −35.7 (*c* = 1.63, $CHCl_3$).

Allylic Amine 16h. As per amine **16i** starting from azide **5h** (1.00 g, 1.88 mmol), $LiAlH_4$ (powder 95%, 107 mg, 2.82 mmol) to afford **16h** as a colorless oil (820 mg, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67−7.65 (m, 4H), 7.44−7.34 (m, 6H), 5.39−5.22 (m, 2H), 3.64 (t, 2H, J = 6.6 Hz), 3.12−3.22 (m, 1H), 1.89−1.24 (m, 12H), 1.04 (s, 9H), 1.01−0.65 (m, 6H), 0.85 (d, 3H, J = 7.2 Hz), 0.84 (d, 3H, J = 6.6 Hz), 0.69 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75.5 MHz, C_6D_6) δ (ppm) 135.6 (s), 135.1 (s), 134.0, (s), 129.5 (s), 127.7 (s), 63.7 (t), 53.9 (s), 47.2 (s), 44.4 (s), 43.5 (t), 37.9 (t), 35.2 (t), 32.7 (t), 32.5 (s), 28.0 (s), 26.9 (t), 24.2 (q), 21.4 (t), 19.1 (q), 15.4 (q). IR (neat, cm^{-1}): 3891, 3366, 3070, 2955, 2929, 2859, 1472, 1428, 1111, 971. LRMS (*m*/*z*, (relative intensity)): 506 ([MH]$^+$, 84), 489 (49), 448 (100), 293 (30), 194 (100), 137 (13), 95 (8). HRMS calcd for $C_{33}H_{51}NOSi$: 505.3740, found: 505.3731. $[\alpha]^{20}_D$ = −20.5 (*c* = 2.34, $CHCl_3$).

Allylic Amine 16i. Lithium aluminum hydride (595 mg, 14.9 mmol) was added portion wise to the azide **5i** (4.16 g, 9.86 mmol) in diethyl ether (100 mL) at 0 °C. The mixture was stirred, allowed to slowly warm up to RT for 13 h and then quenched with water (0.6 mL), a 15% NaOH aqueous solution (0.6 mL) and water (1.8 mL). The mixture was stirred 20 min at RT and then stirred with anhydrous Na_2SO_4 for 30 min. The mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (20% ethyl acetate in hexanes saturated with NH_4OH) to yield pure amine **16i** (3.50 g, 90%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.30−5.17 (m, 2H), 3.75−3.66 (m, 1H), 3.17−3.15 (m, 1H), 1.87−1.76 (m, 2H), 1.68−1.63 (m, 1H), 1.56−1.42 (m, 4H), 1.41−1.19 (m, 7H), 1.06 (d, 3H, J = 6.0 Hz), 1.01−0.70 (m, 7H), 0.83 (s, 9H), 0.81 (d, 3H, J = 6.6 Hz), 0.65 (d, 3H, J = 6.6 Hz), −0.01 (s, 6H). IR (neat) • (cm^{-1}) 2958, 2934, 2864, 1468, 1378, 1256, 1139, 838, 777. LRMS (*m*/*z*, relative intensity) 395 ([M$^+$], 1), 380 ([M$^+$ − CH_3], 2), 338 ([M$^+$ − C_4H_9] 5), 194 (100). HRMS calcd for $C_{24}H_{49}NOSi$: 395.3583, found: 395.3591. $[\alpha]^{20}_D$ = −30.5 (*c* = 1.13, $CHCl_3$).

***t*-Butyl Carbamate 22h.** In a 100 mL r.b. flask was dissolved the amine **16h** (1.575 g, 3.114 mmol) in acetonitrile (31.5 mL). Anhydrous K_2CO_3 (452 mg, 3.270 mmol) was added into the solution, and this solution was stirred 5 min at RT. Then, the allyl bromide (414 mg, 3.425 mmol) was added very slowly (20 μL/min) and the resulting suspension was stirred at RT for 1.5 h and an excess of allyl bromide (0.2 eq.) was added. The resulting

mixture in stirred again for a another 2 h at RT, diluted in H_2O and extracted with 3 portions of EtOAc. The combined organic extracts were washed once with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil. The crude product was purified on silica gel with 1:1/Et_2O: Hexanes as eluant to afford alkylated amine as a colorless oil (986 mg, 59%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (dd, 4H, J = 7.7, 1.7 Hz), 7.44−7.34 (m, 6H), 5.91 (ddt, 1H, J = 17.0, 16.5, 6.1 Hz), 5.27 (dd, 1H, J = 15.4, 8.8 Hz), 5.17−5.07 (m, 3H), 3.63 (t, 2H, J = 6.6 Hz) 3.28 (dd, 1H, J = 8.3−5.5 Hz)), 3.12 (dd, 1H, J = 13.8, 6.6 Hz), 3.02−2.90 (m, 1H), 1.98−1.83 (m, 2H), 1.74−1.67 (m, 1H), 1.59−1.24 (m, 10H), 1.04 (s, 9H), 1.02−0.64 (m, 3H), 0.87 (d, 6H, J = 6.6 Hz), 0.83 (d, 3H, J = 6.6 Hz), 0.70 (d, 3H, J = 6.6 Hz). IR (neat, cm^{-1}): 3071, 2945, 2930, 2859, 1471, 1455, 1427, 1111, 909. LRMS (*m/z*, (relative intensity)): 545 ([M$^+$], 2), 504 (23), 488 (31), 234 (100), 199 (18), 183 (10), 96 (43). HRMS calcd for $C_{36}H_{55}NOSi$: 545.4053, found 545.4038. $[\alpha]^{20}_D = -21.7$ (c 1.09, $CHCl_3$).

In a 100 mL r.b. flask was dissolved the amine (1.31 g, 2.40 mmol) in DMF (20 mL) and this solution was stirred at RT for 5 min. Then, triethylamine (368 mg, 3.60 mmol) was added and this solution was stirred for another 5 min at RT and the di-*t*-butyldicarbonate (786 mg, 3.60 mmol) was added and this resulting mixture was stirred at RT during 23 h. The mixture was then treated with a saturated solution of NH_4Cl and the aqueous phase was extracted with 3 portions of EtOAc and the combined organic extracts were washed once with water and once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. The crude product was purified on silica gel with 3:97/AcOEt:Hexanes as eluant to afford the butoxy carbamate **22h** a colorless oil (1.39 g, 92%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (dd, 4H, J = 7.7, 1.7 Hz), 7.44−7.34 (m, 6H), 5.82−5.70 (m, 1H), 5.40−5.23 (m, 2H), 5.10−5.00 (m, 2H), 3.63 (t, 2H, J = 6.6 Hz), 1.90−1.76 (m, 2H), 1.72−1.67 (m, 1H), 1.61−1.51 (m, 4H), 1.44 (s, 9H), 1.35−1.25 (m, 6H), 1.04 (s, 9H), 0.97−0.79 (m, 6 H), 0.84 (d, 6H, J = 6.6 Hz), 0.67 (d, 3H, J = 6.6 Hz). LRMS (*m/z*, (relative intensity)): 589 ([M − C_4H_9]$^+$, 1), 532 (44), 455 (61), 282 (51), 278 (100), 235 (70), 199 (41), 140 (49). HRMS calcd for $C_{37}H_{55}NO_3Si$: 589.3951, found 589.3942.

Pyrrolidine 23h. In a 500 mL r.b. flask was dissolved the butyl carbamate **22h** (1.00 g, 1.55 mmol) in CH_2Cl_2 (310 mL, 0.005 M) and the reaction was refluxed for 10 min. The reflux was stopped and the Grubbs catalyst (63.7 mg, 0.077 mmol) was added in small portions and the reaction mixture was refluxed for 18 h. The resulting solution was concentrated under reduced pressure and the crude product was purified on silica gel with 1:20/EtOAc:Hexanes as eluant to afford pyrrolidine **23h** as a colorless oil (743 mg, 100%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (dd, 4H, J = 7.7, 2.2 Hz), 7.44−7.33 (m, 6H), 5.75−5.68 (bd, 2H, J = 6.6 Hz), 4.50 (m, 1H), 4.17(bd, 1H, J = 13.2 Hz), 3.98 (dd, 4H, J = 9.9, 5.5 Hz), 3.63 (t, 2H, J = 6.6 Hz), 1.69−1.51 (m, 4H), 1.46 (s, 9H), 1.35−1.24 (m, 2H), 1.04 (s, 9H). IR (neat, cm^{-1}): 3071, 2861, 1704, 1697, 1427, 1392, 1174, 1111, 910. LRMS (*m/z*, (relative intensity)): 480 ([MH]$^+$, 39), 380 (62), 366 (58), 288 (49), 244 (16), 83 (100). HRMS calcd for $C_{29}H_{42}NO_3Si$: 480.2934, found 480.2942 (for [MH]$^+$). $[\alpha]^{20}_D = +3.5$ (c = 1.25, $CHCl_3$).

Amide 27i. 3-Butenoic acid (0.83 mL, 9.74 mmol) was added to a solution of the amine **16i** (3.49 g, 8.83 mmol), *N*,*N*′-dicyclohexylcarbodiimide (2.00 g, 9.69 mmol) and 4-(dimethylamino)pyridine (184 mg, 1.51 mmol) in dichloromethane (52 mL) at 0 °C. The mixture was stirred 2 h at 0 °C before the addition of an additional quantity of 3-butenoic acid (0.3 mL, 3.58 mmol). The mixture was stirred at 0 °C for 45 min and then concentrated under reduce pressure. The resulting solid was triturated once with hexanes. The solid was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (20% ethyl acetate in hexanes) to yield pure amide **27i** (4.03 g, 99%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.88 (ddt, 1H, J = 16.9, 10.1, 7.2 Hz), 5.56−5.54 (m, 1H), 5.35−5.14 (m, 4H), 4.34 (quint, 1H, J = 6.9 Hz), 3.71 (sext, 1H, J = 6.0 Hz), 2.94 (d, 2H, J = 7.2 Hz), 1.87−1.65 (m, 3H), 1.58−1.19 (m, 9H), 1.05 (d, 3H, J = 6.0 Hz), 0.97−0.72 (m, 10H), 0.84 (s, 9H), 0.63 (d, 3H, J = 7.2 Hz), −0.01 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 169.3 (s), 136.6 (d), 131.6 (d), 128.9 (d), 119.4 (t), 68.5 (d), 50.8 (d), 47.0 (d), 44.4 (d), 43.0 (t), 41.8 (t), 39.4 (t), 35.3 (t), 35.1 (t), 32.4 (d), 27.9 (d), 25.9 (q), 24.0 (t), 23.8 (q), 22.5 (q), 21.9 (t), 21.4 (q), 18.1 (s), 15.3 (q), −4.5 (q), −4.7 (q). IR (neat) • (cm^{-1}) 3273 (large), 2957, 2928, 2853, 1641, 1547, 1457, 1367, 1250, 830, 769. LRMS (*m/z*, relative intensity) 463 ([M$^+$], 20), 448 ([M$^+$ − CH_3], 5), 406 ([M$^+$ − C_4H_9], 100). HRMS calcd for $C_{28}H_{53}NO_2Si$: 463.3845, found: 463.3835. $[\alpha]^{20}_D = -41.9$ (c = 0.48, $CHCl_3$).

Dihydropyridinone 28i. A refluxing solution of amide **27i** (702 mg, 1.51 mmol) in dichloromethane (700 mL) was bubbled with argon for 30 min. Dichlorophenylborane (0.19 mL, 1.45 mmol) and Grubbs second generation catalyst (65 mg, 0.077 mmol) were respectively added at RT and the mixture was refluxed for 2 h. The mixture was cooled down to RT and a solution of concentrated HCl aqueous solution and methanol (1:99, 8 mL) was added. The mixture was stirred for 16 h and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (from 5 to 10% methanol in ethyl acetate) followed by an activated carbon treatment to yield pure alcohol **28i** (277 mg, 100%) as a colorless oil. Diastereomer A (α or β OH): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.93 (s, 1H), 5.66−5.55 (m, 2H), 4.02−3.92 (m, 1H), 3.73−3.44 (m, 2H), 2.82−2.76 (m, 2H), 1.58−1.29 (m, 6H), 1.07 (d, 3H, J = 6.0 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 170.8 (s), 125.8 (d), 121.4 (d), 66.8 (d), 53.4 (d), 38.4 (t), 36.6 (t), 30.9 (t), 23.2 (q), 19.9 (t). Diastereomer B (α or β OH): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.10 (s, 1H), 5.66−5.55 (m, 2H), 4.02−3.92 (m, 1H), 3.73−3.44 (m, 2H), 2.82−2.76 (m, 2H), 1.58−1.29 (m, 6H), 1.07 (d, 3H, J = 5.0 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 170.8 (s), 125.6 (d), 121.2 (d), 67.2 (d), 53.0 (d), 38.4 (t), 36.3 (t), 30.9 (t), 23.8 (q), 20.9 (t). IR (neat) • (cm^{-1}) 3541−3122, 3046, 2969, 2928, 2863, 1682, 1658, 1410, 1346, 1139. LRMS (*m/z*, relative intensity) 183 ([M$^+$], 5), 182 ([M$^+$ − H], 10), 96 (100). HRMS calcd for $C_{10}H_{17}NO_2$: 183.1259, found: 183.1252. $[\alpha]^{20}_D = +40.8$ (c = 1.22, $CHCl_3$).

Epoxide 34. In a 50 mL r.b. flask was dissolved the pyrrolidine adduct **23h** (500 mg, 1.04 mmol) in acetonitrile (10.0 mL) and a 0.0004 M solution of Na_2•EDTA (5.20 mL, 0.002 mmol) was added. The reaction mixture was cooled to 0 °C and trifluoacetone (2.00 mL, 2.51 g, 22.4 mmol) was added. Anhydrous $NaHCO_3$ (1.36 g, 16.2 mmol) and Oxone (6.41 g, 10.4 mmol) were mixed together and added by small portions over 1.4 h keeping the temperature at 0 °C. The reaction mixture was then stirred at 0 °C for 1.5 h, at RT for 17 h and then diluted with H_2O. The aqueous phase was extracted with 3 portions of DCM and the combined organic extracts were washed once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. The crude product was purified on silica gel with 1:4/AcOEt:Hexanes as eluant to afford a colorless oil (460 mg, 89%). Rotamer 1: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (dd, 4H, J = 7.4, 1.9 Hz), 7.45−7.35 (m, 6H), 4.05 (t, 1H, J = 5.8 Hz), 3.88 (d, 1H, J = 13.2 Hz), 3.66 (dt, 2H, J = 6.1, 2.2 Hz), 3.58 (d, 1H, J = 3.3 Hz), 3.43 (d, 1H, J = 3.3 Hz), 3.22 (d, 1H, J = 3.3 Hz), 1.60−1.43 (m, 6H), 1.42 (s, 9H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) 155.1 (s), 135.6 (d), 133.9 (s), 129.6 (d), 127.6 (d), 63.6 (t), 58.5 (d), 57.8 (d), 54.9, 47.1 (t), 33.1 (s), 32.6 (t), 30.9 (t), 28.4 (q), 26.9 (q), 21.9 (t), 19.2 (s). Rotamer 2: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (dd, 4H, J = 7.4, 1.9 Hz), 7.45−7.35 (m, 6H), 3.95 (t, 1H, J = 5.8 Hz), 3.78 (d, 1H, J = 12.7 Hz), 3.66 (dt, 2H, J = 6.1, 2.2 Hz), 3.56 (d, 1H, J = 3.3 Hz), 3.41 (d, 1H, J = 3.3 Hz), 3.20 (d, 1H, J = 3.3 Hz), 1.60−1.43 (m, 6H), 1.42 (s, 9H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) 155.1 (s), 135.6 (d), 133.9 (s), 129.6 (d), 127.6 (d), 63.6 (t), 58.1 (d), 57.5 (d), 54.3 (d), 46.5 (t), 33.1 (s), 32.6 (t), 30.2 (t), 28.4 (q), 26.9 (q), 21.9 (t), 19.2 (s). IR (neat, cm^{-1}): 3069, 3049, 2933, 2860, 1697, 1427, 1389,

1173, 1113. LRMS (*m/z*, (relative intensity)): 513 ($[MNH_4]^+$, 14), 496 ($(MH)^+$, 100), 440 (90), 396 (70), 362 (48), 304 (33). HRMS calcd for $C_{29}H_{42}NO_4Si$ $[MH]^+$: 496.2883, found 496.2873. $[\alpha]^{20}_D = +27.6$ ($c = 0.99$, $CHCl_3$).

In a 25 mL r.b. flask was dissolved the above epoxide (440 mg, 0.888 mmol) in anhydrous THF (8.8 mL). This solution was cooled to 0 °C and TBAF (1.0 M in THF, 0.976 mL, 0.976 mmol) was added. The reaction mixture was stirred at RT for 4.5 h and quenched with H_2O and 1N aqueous solution of HCl. The aqueous phase was extracted with 3 portions of Et_2O and the combined organic extracts were washed once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. The crude product was purified on silica gel with 2:3 to 7:3/AcOEt:Hexanes as eluant to afford a colorless oil (198 mg, 87%). Rotamer 1: ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 4.08 (t, 1H, $J = 6.1$ Hz), 3.88 (d, 1H, $J = 13.2$ Hz), 3.65 (t, 2H, $J = 6.1$ Hz), 3.61 (d, 1H, $J = 2.7$ Hz), 3.46 (s, 1H), 3.24 (d, 1H, $J = 13.2$ Hz), 1.72 (br s, 1H), 1.68−1.47 (m, 6H), 1.43 (s, 9H). Rotamer 2: ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 3.98 (t, 1H, $J = 6.1$ Hz), 3.79 (d, 1H, $J = 13.2$ Hz), 3.65 (t, 2H, $J = 6.1$ Hz), 3.58 (d, 1H, $J = 2.7$ Hz), 3.46 (s, 1H), 3.24 (d, 1H, $J = 13.2$ Hz), 1.72 (br s, 1H), 1.68−1.47 (m, 6H), 1.43 (s, 9H). IR (neat, cm^{-1}): 3728−3026, 2976, 2944, 2930, 2870, 1682, 1424, 1392, 1174, 1119. LRMS (*m/z*, (relative intensity)): 258 ($[MH]^+$, 78), 202 (100), 158 (100), 140 (37), 122 (15), 112 (30), 84 (50). HRMS calcd for $C_{13}H_{23}NO_4$: 257.1627, found 257.1617. $[\alpha]^{20}_D = +40.6$ ($c = 0.70$, $CHCl_3$).

The alcohol (500 mg, 1.94 mmol) and pyridine (204 μL, 200 mg, 2.53 mmol) were dissolved in dichloromethane (10.0 mL). The solution was stirred for 10 min, upon which time tosyl chloride (445 mg, 2.33 mmol) was added. The reaction mixture was stirred 26 h at RT, upon which time water and a saturated aqueous solution of $NaHCO_3$ were added. The organic phase was separated and extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product was purified on silica gel with 7:3/AcOEt:Hexanes as eluant to afford epoxide **34** as a colorless oil (683 mg, 85%). Rotamer 1: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.78 (d, 2H, $J = 7.7$ Hz), 7.35 (d, 2H, $J = 7.7$ Hz), 4.02 (t, 2H, $J = 6.1$ Hz), 4.01 (t, 1H, $J = 6.1$ Hz), 3.89 (d, 1H, $J = 13.2$ Hz), 3.59 (d, 1H, $J = 3.6$ Hz), 3.40 (d, 1H, $J = 3.6$ Hz), 3.22 (d, 1H, $J = 9.6$ Hz), 2.45 (s, 3H), 1.73−1.64 (m, 2H), 1.57−1.36 (m, 6H), 1.42 (s, 9H). Rotamer 2: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.78 (d, 2H, $J = 7.7$ Hz), 7.35 (d, 2H, $J = 7.7$ Hz), 4.02 (t, 2H, $J = 6.1$ Hz), 3.95 (t, 1H, $J = 6.1$ Hz), 3.78 (d, 1H, $J = 13.2$ Hz), 3.58 (d, 1H, $J = 3.6$ Hz), 3.38 (d, 1H, $J = 3.6$ Hz), 3.18 (d, 1H, $J = 9.6$ Hz), 2.45 (s, 3H), 1.73−1.64 (m, 2H), 1.57−1.36 (m, 6H), 1.42 (s, 9H). IR (neat) υ (cm^{-1}): 3040, 2972, 2939, 2873, 1699, 1599, 1420, 1389, 1172, 1118. LRMS (*m/z*, relative intensity): 429 ($[MNH_4]^+$, 4), 412 ($[MH]^+$, 11), 373 (86), 258 (60), 237 (90), 202 (88), 140 (100), 84 (85). HRMS calcd for $C_{20.5}HNO_6S$ $(MH)^+$: 412.1794, found 412.1785. $[\alpha]^{20}_D = +34.9$ ($c = 0.55$, $CHCl_3$).

Indolizidine 35. Tosylate **34** (680 mg, 1.65 mmol) was dissovled in dichloromethane (4.0 mL), and trifluoroacetic acid (0.80 mL) was added dropwise. The reaction mixture was stirred at RT for 1 h and was then concentrated under reduced pressure. The residue was coazeotroped with benzene (2 × 5 mL) to remove most of the water. It was then taken up in dichloromethane (10.2 mL) and triethylamine (1.40 mL, 1.01 g, 9.91 mmol) was added. The mixture was stirred at RT for 18 h and was then concentrated under reduced pressure. The resulting oil was taken up in dioxane (2.0 mL), and a 5N aqueous solution of NaOH (0.5 mL, 2.45 mmol) was added to remove the tosyl salts. This mixture was stirred for 1 h at RT and was then concentrated under reduced pressure. The crude product was purified on silica gel eluting with a mixture of methanol, dichloromethane, and a 30% solution of NH_4OH (15:84: 1). Compound **35** was obtained as colorless oil (145 mg, 63%). ^{1}H NMR (300 MHz, CD_3OD): δ (ppm) 3.62 (d, 1H, $J = 2.8$ Hz), 3.47 (d, 1H, $J = 2.8$ Hz), 3.12 (dd, 1H, $J = 12.1$, 3.9 Hz), 2.91−2.85 (m, 1H), 2.80 (dd, 1H, $J = 12.1$, 2.8 Hz), 1.83−1.77 (m, 2H), 1.53−1.40 (m, 3H), 1.38−1.29 (m, 2H), 1.16 (dt, 1H, $J = 12.5$, 3.9 Hz). IR (neat) υ (cm^{-1}): 3625−3105, 3032, 2926, 2851, 2805, 1443, 1175, 1139. LRMS (*m/z*, relative intensity): 139 ($[M]^+$, 39), 120 (20), 83 (88), 55 (100), 41 (41). HRMS calcd for $C_8H_{13}NO$: 139.0997, found 139.1002. $[\alpha]^{20}_D = +16.3$ ($c = 0.95$, MeOH).

Lentiginosine (+)-30. Indolozidine **35** (130 mg, 0.934 mmol) was dissolved in a mixture of dioxane (1.0 mL) and a 10% mixture of H_2SO_4 (1.0 mL). The reaction mixture was refluxed for 6 h, and then cooled to RT and directly purified by silical gel column flash chromatography eluting with a mixture of methanol, dichloromethane, and 30% NH_4OH (15:84: 1). A white solid (104 mg, 71%) was obtained. m.p. 98−100 °C.^{1}H NMR (300 MHz, D_2O): δ (ppm) 4.06 (ddd, 1H, $J = 7.7$, 3.9, 1.7 Hz), 3.64 (dd, 1H, $J = 8.8$, 3.9 Hz), 2.94 (br d, 1H, $J = 11.0$ Hz), 2.83 (dd, 1H, $J = 11.0$, 1.7 Hz), 2.62 (dd, 1H, $J = 11.0$, 7.7 Hz), 2.05 (td, 1H, $J = 11.6$, 3.3 Hz), 1.99−1.91 (m, 2H), 1.82−1.79 (m, 1H), 1.63 (br d, 1H, $J = 13.2$ Hz), 1.52−1.37 (m, 1H), 1.32−1.17 (m, 2H). IR (NaCl/$CHCl_3$) υ (cm^{-1}): 3529−3514, 3021, 3012, 2942, 2857, 2806, 1443, 1212, 1140. LRMS (*m/z*, relative intensity): 158 ($[MH]^+$, 100), 140 (10), 97 (44). HRMS calcd for $C_8H_{16}NO_2$ $[MH]^+$: 158.1181, found 158.1177. $[\alpha]^{20}_D = +2.4$ ($c = 0.41$, MeOH).

Iodide 38. Triethylamine (0.55 mL, 3.95 mmol) and methanesulfonyl chloride (0.25 mL, 3.23 mmol) were added to a solution of the alcohol **28i** (360 mg, 1.97 mmol) in THF (16 mL) at 0 °C. The mixture was stirred 16 h at RT and quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were washed once with brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (from 0 to 5% methanol in ethyl acetate) to yield pure mesylate (496 mg, 97%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.57 (s, 1H), 5.72 (dtd, 1H, $J = 9.9$, 3.2, 1.5 Hz), 5.63−5.58 (m, 1H), 4.74 (sext, 1H, $J = 6.0$ Hz), 4.07−4.02 (m, 1H), 2.96 (s, 3H), 2.85−2.81 (m, 2H), 1.74−1.39 (m, 6H), 1.36 (d, 3H, $J = 6.0$ Hz). IR (neat) • (cm^{-1}) 3217, 3046, 2987, 2934, 2863, 1676, 1665, 1464, 1334, 1169, 915. LRMS (*m/z*, relative intensity) 261 ($[M^+]$, 2), 182 ($[M^+ - CH_3SO_2]$, 5), 166 ($[M^+ - CH_3SO_3]$, 30), 96 (100). HRMS calcd for $C_{11}H_{19}NO_4S$: 261.1035, found: 261.1040. $[\alpha]^{20}_D = +48.9$ ($c = 2.06$, $CHCl_3$).

The above mesylate (490 mg, 01.88 mmol), sodium iodide (2.86 g, 19.1 mmol), and $NaHCO_3$ (1.63 g, 19.4 mmol) were stirred 18 h in acetone (8.5 mL), and the mixture was quenched with water (25 mL). The aqueous layer was extracted with ethyl acetate (4 × 25 mL), and the combined organic layers were washed once with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (from 0 to 5% methanol in ethyl acetate) to yield pure iodide **38** (450 mg, 82%) as a colorless oil. ^{1}H NMR Diastereomer A (300 MHz, $CDCl_3$) δ (ppm) 7.05−7.01 (m, 1H), 5.77 (dtd, 1H, $J = 9.9$, 3.2, 1.5 Hz), 5.69−5.64 (m, 1H), 4.19−4.07 (m, 2H), 2.92−2.88 (m, 2H), 1.90 (d, 3H, $J = 7.2$ Hz), 1.87−1.77 (m, 2H), 1.66−1.38 (m, 4H). ^{1}H NMR Diastereomer B (300 MHz, $CDCl_3$) δ (ppm) 7.05−7.01 (m, 1H), 5.77 (dtd, 1H, $J = 9.9$, 3.2, 1.5 Hz), 5.69−5.64 (m, 1H), 4.19−4.07 (m, 2H), 2.92−2.88 (m, 2H), 1.90 (d, 3H, $J = 6.0$ Hz), 1.87−1.77 (m, 2H), 1.66−1.38 (m, 4H). IR (neat) υ (cm^{-1}) 3209, 3049, 2918, 2870, 1677, 1663, 1338. LRMS (*m/z*, relative intensity) 293 ($[M^+]$, 1), 197 ($[M^+ - C_5H_6NO]$, 5), 166 ($[M^+ - I]$, 20), 96 (100). HRMS calcd for $C_{10}H_{16}INO$: 293.0277, found: 293.0269. $[\alpha]^{20}_D = +66.4$ ($c = 1.40$, $CHCl_3$).

Perhydroquinolinone 39. A refluxing solution of iodide **38** (450 mg, 1.54 mmol) in benzene (980 mL) was bubbled with argon for 30 min. Tributyltin hydride (0.54 mL, 2.0 mmol) in benzene (20 mL) and AIBN (77 mg, 0.47 mmol) were added and the mixture was refluxed 12 h. The tributyltin hydride solution was added with a seringe pump in 4 h after an initial addition of 3 mL. AIBN was added in seven portions at each hour. The solution was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (from 50% hexanes in ethyl acetate

to 100% ethyl acetate to 10% methanol in ethyl acetate) to yield the known perhydroquinolinone **39** (64 mg, 25%) as a white solid.[30] m.p. 108−110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.40−5.30 (m, 1H), 3.63 (q, 1H, J = 3.3 Hz), 2.32−2.28 (m, 2H), 2.10−2.01 (m, 1H), 1.73−1.41 (m, 9H), 0.93 (d, 3H, J = 6.6 Hz). IR (neat) υ (cm^{-1}) 3390, 2940, 2869, 1646, 1461, 1319. LRMS (*m*/*z*, relative intensity) 167 (M^+, 20), 152 (M^+-CH_3, 5), 124 (M^+-CHNO, 100). HRMS calcd for $C_{10}H_{17}NO$: 167.1310, found: 167.1314. $[\alpha]^{20}_D$ = +33.8 (c = 0.08, $CHCl_3$).

Pumiliotoxin C, Hydrochloride Salt ((+)-31·HCl). The perhydroquinolinone **39** (31 mg, 0.19 mmol) in d_2-dichloromethane (1 mL) was added to a solution of trimethyloxonium tetrafluoroborate (53 mg, 0.36 mmol) and diisopropylethylamine (1 drop) in d_2-dichloromethane (1 mL). The mixture was stirred 1 h at RT and quenched with a saturated $NaHCO_3$ aqueous solution (2 mL) at 0 °C. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to yield the crude imino ether (49 mg) used quickly to avoid degradation.

A solution of propylmagnesium bromide in benzene (0.9 M, 1 mL, 0.9 mmol) was added to a solution of imino ether (49 mg, 0.36 mmol) in benzene (3 mL). The mixture was stirred 4 h in a sealed vial at 85 °C. The reaction mixture was cooled down to 0 °C, dropped in diethyl ether (5 mL), and quenched with a saturated $NaHCO_3$ aqueous solution (5 mL). The aqueous layer was extracted with diethyl ether (2 × 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The imine (30 mg) was used quickly to avoid degradation.

The imine (30 mg, 0.16 mmol) and 5% palladium on carbon were stirred at RT in methanol (5 mL) under hydrogen atmosphere for 40 h at RT. The mixture was filtered on Celite and gaseous HCl was bubbled in the resulting solution. The mixture was concentrated under reduced pressure and the crude solid was recrystallized in isopropyl alcohol-diethyl ether to yield pure HCl salt of pumiliotoxin C ((+)-31·HCl) (22 mg, 59% for 3 steps) as white crystals. m.p. 228−230 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.57 (s, 1H), 8.37 (s, 1H), 3.33−3.29 (m, 1H), 2.99−2.95 (m, 1H), 2.51−2.35 (m, 2H), 2.17−2.07 (m, 4H), 1.86 (d, 1H, J = 12.7 Hz), 1.78 (d, 1H, J = 13.2 Hz), 1.63−1.27 (m, 6H), 1.25−1.20 (m, 1H), 1.01−0.98 (m, 1H), 0.92 (t, 3H, J = 6.3 Hz), 0.89 (d, 3H, J = 5.5 Hz). LRMS (*m*/*z*, relative intensity) 195 ([M^+], 3), 194 ([M^+ − H], 3), 152 ([M^+ − C_3H_7], 100). HRMS calcd for $C_{13}H_{25}N$: 195.1987, found: 195.1982. $[\alpha]^{20}_D$ = +12.9 (c = 0.41, $CHCl_3$).

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Supporting Information Available: Experimental procedures and ^{1}H NMR spectra for all new compounds not included in the Experimental Section of the article. Crystallographic data for compound **18n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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