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Synthesis of Fused Piperidinones through a Radical-Ionic Cascade

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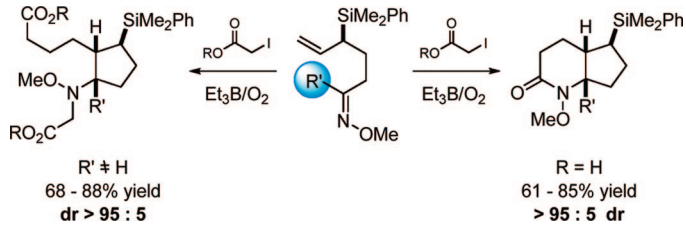
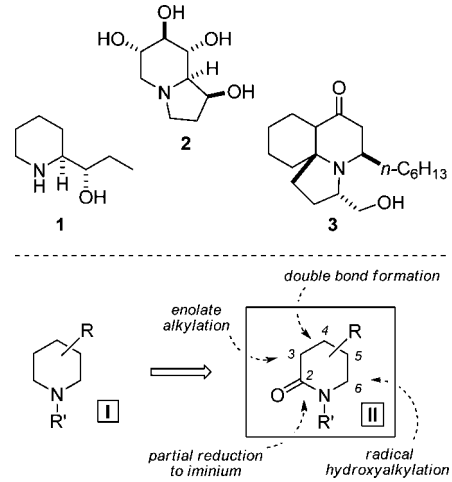


Azabicyclo[4.3.0]nonanes were assembled, from chiral allylsilanes possessing an oxime moiety, using a stereocontrolled formal [2 + 2 + 2] radical-ionic process. The cascade involves the addition of an α-iodoester to the less substituted end of the enoxime which is then followed by a 5-*exo-trig* cyclization onto the aldoxime function, producing an alkoxyaminyl radical species which finally lactamizes to afford the titled piperidinone. High levels of stereoinduction were observed, demonstrating the ability of a silicon group located at the allylic position to efficiently control the stereochemistry of the two newly created stereogenic centers. When the radical cascade was extended to ketoximes, the resulting sterically hindered alkoxyaminyl radical did not react further with the initiator Et_3B to produce the expected nucleophilic amidoborane complex. In sharp contrast, this long-lived radical recombined with the initial α-stabilized ester radical to produce a cyclopentane incorporating two ester fragments.

Introduction

The piperidine skeleton, as in (*β*)-conhydrine **1**, is ubiquitous in Nature[1] and is also found as a key structural motif in many synthetic pharmaceutical leads.[2] This common heterocycle may also be fused with other rings as seen, for example, in indolizidines (i.e., castanospermine **2**) which have been of widespread interest given their attractive glycosidase inhibitory activities.[3,4] The piperidine skeleton may also be imbedded in fairly complex tricyclic alkaloids, such as in lepadiformine **3** and related analogues[5] (Scheme 1). The control of the relative configuration at the ring junction as well as the stereochemistry of the quaternary center in targets such as **3** constitute two of the key problems encountered in the syntheses of these alkaloids. Several elegant solutions to these stereochemical issues have nevertheless been accomplished during the course of their total

SCHEME 1. Piperidinones as Valuable Precursors for Natural Product Synthesis



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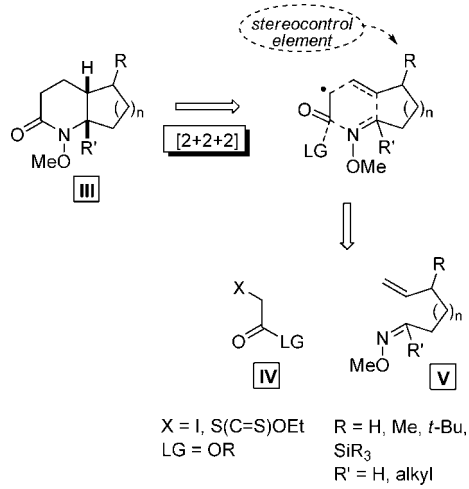
SCHEME 2. A formal [2 + 2 + 2] Process for the Synthesis of Piperidinones



syntheses.[5] Piperidinones of type **II** may be considered as simple precursors for the construction of the polysubstituted piperidine skeleton **I**. Structure **II** may be easily functionalized at any position through well-known methods, including alkylation at C3,[6] transformation into an α,β unsaturated amide,[6a] partial reduction of the C=O bond into versatile iminium intermediates,[7] or recently developed radical-mediated hydroxyalkylation at C6.[8] A chiral auxiliary may also be introduced on the nitrogen atom allowing a ready access to enantiopure analogues.[9] Therefore, as virtually all carbon centers may be functionalized, piperidinones **II** constitute valuable intermediates en route to the synthesis of more complex piperidines.

We recently reported[10] on a straightforward one-pot synthesis of fused piperidinones **III** via a formal [2 + 2 + 2] radical-ionic cyclization of enoximes **V** (Scheme 2).[11] We describe here a full account of these investigations, focusing on various aspects of our research, including: (1) the stereocontrolled generation of the azabicyclo[4.3.0]nonane skeleton **III** through 1,2- and 1,3-induction and (2) an unexpected tandem addition−cyclization−recombination process. Our piperidinones may be easily accessible starting from structurally simple enoximes **V** having an allylic stereocenter and a simple α-haloester or xanthate **IV**. The substituent at the allylic position is central to the methodology as it is expected to dictate the relative configuration of the three contiguous stereogenic centers during the 5-*exo-trig* cyclization. This would allow the controlled installation of the ring junction, a problem which, until recently, had not received satisfying answers using radical-mediated processes.[12] The two-carbon building block, incorporating the carbonyl unit would be generated from the corresponding α-iodo, α-bromo, or α-xanthate ester **IV**, identified as the electron-poor radical partner.[13] Addition of such radicals onto olefins is known to be an efficient process, providing a new radical intermediate that can then cyclize in a 5- or 6-*exo-trig* mode onto the oxime moiety. Such cyclizations, pioneered by Corey[14] and Bartlett[15] and later developed by Naito,[16] Marco-Contelles,[17] and others,[18] are faster than the corresponding cyclizations onto olefins.[19] We envisaged that the formation of the ring should be followed by the reaction of the resulting alkoxyaminyl radical with a suitable radical mediator[20] (Et_3B or Et_2Zn). In the event, this radical polar crossover reaction would provide a nucleophilic boron or zinc amide complex which could then cyclize to afford the desired piperidinone **III**.

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SCHEME 3. Enoximes 4−10

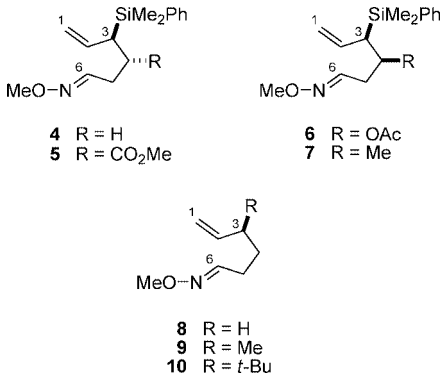
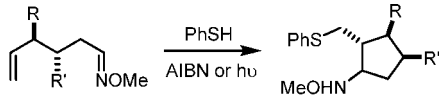


TABLE 1. Influence of an Allylic Silicon Group on the Course of the Thiyl Addition−5-*Exo-Trig* Cyclization onto Enoxime 6 and 8



8 R = R' = H — **11a** : **11b**

6 R = $SiMe_2Ph$, R' = OAc — **12a** : **12b**

entry	oxime	*T* (°C)	*cis/trans* **a**:**b**[a]	yield[d] (%)
1	**8**	80[a]	77:23	49
2	**6**	80[a]	89:11	77
3	**8**	25[b]	nd	<10
4	**6**	25[b]	89:11	95
5	**6**	−10[b]	92:8	69 (99)
6	**6**	−40[b]	>95:5	32 (99)
7	**6**	−78[b]	>95:5	22 (92)

[a] Initiation with AIBN. [b] Initiation with *hν* (sunlamp). [c] Estimated from ^{1}H NMR of the crude mixture. [d] Isolated yields (yield based on recovered starting material).

Results and Discussion

Ene−Aldoxime Precursors. Our laboratory has previously shown for related 5-*exo-trig* cyclization of 1,6-dienes that allylic silicon groups efficiently control the relative configuration both at the ring junction and at proximal stereogenic centers.[12a−c] It was reasoned that a similar behavior might be expected with enoximes. We therefore embarked on the preparation of a series of chiral allylsilanes **4**−**7** possessing an oxime moiety at C6. In order to evaluate the impact of the silicon substituent on stereoselectivity, we also prepared enoxime **8** devoid of any allylic chiral center and enoximes **9** and **10** which possess respectively a methyl and a sterically demanding *tert*-butyl group at C3 (Scheme 3) (see the Supporting Information for preparation of these substrates).[10]

Thiyl Radical Addition onto Chiral Allylsilanes Oximes. Prior to embarking on the design of a formal [2 + 2 + 2] cascade as depicted in Scheme 2, we first investigated the tandem addition-5-*exo-trig* cyclization of thiyl radicals on enoxime **V** (see Scheme 2), in order to test the feasibility of the first two steps of the process (Table 1). Electrophilic thiyl radicals are known to add onto enoximes to produce the corresponding five-membered ring through a 5-*exo-trig* cyclization, with generally modest levels of stereocontrol.[16e,21] These addition−cyclization sequences were performed on allylsilane **6** and its nonsubstituted counterpart **8** in order to evaluate the effect of an allylic silicon group on the reactivity of the olefin and on the stereochemical course of the reaction. The cyclization was first performed using AIBN as an initiator at 80 °C in benzene. Under these conditions, the simplest model **8**, lacking an allylic stereogenic center, led to a modest stereocontrol in favor of the *cis* isomer **11a**, as previously described by Naito et al. (entry 1).[16e,21] When the same reaction was performed with allylsilane **6**, the desired cyclopentane **12a** was generated with better yield and stereocontrol (entry 2), the *trans,cis* stereoisomer being formed as the major product along with a minute amount of the *trans,trans* isomer which could be separated by chromatography. The structure of *trans,cis* **12a** was unambiguously determined through X-ray diffraction studies (see the Supporting Information). No traces of other stereoisomers were detected on the ^{1}H NMR of the crude reaction mixture. The higher reactivity of allylsilanes toward electrophilic radical species has already been observed by us[10,12a−c] and others[22] and may be ascribed to the enhanced nucleophilic character of allylsilanes as compared to simple olefins mainly due to σ-donation of electrons from the C−Si bond to the π-system of the olefin.[23] Attack of a radical entity on the allylsilane moiety also generates a radical β to silicon (C2) which is known to be stabilized by 2−3 kcal/mol.[24] The excellent 1,2- and good 1,3-stereocontrol occurring during 5-*exo-trig* cyclization of allylsilane−oxime **6** is in line with those reported under similar conditions with 1,6-diene analogues.[12a−c] Finally, photochemical activation allowed the reaction to be carried out at room temperature or lower (entries 3−7), which led to improved diastereocontrol in the case of allylsilane **6**. Complete *trans,cis* selectivity was thus observed at −40 °C, at the expense of the yield (entry 6). A satisfying 92:8 ratio was, however, obtained at −10 °C at 69% conversion (entry 5). It is worth noting that although conversions were not complete, all reactions were extremely clean, the only other component of the crude mixture being unconsumed starting material. In sharp contrast, at room temperature, precursor **8** under irradiation led to a poor conversion to the corresponding aminocyclopentane (entry 3), showing the remarkable "accelerating effect" of an allylic silicon group toward the addition of radicals having an electrophilic character.[12a,b]

[2 + 2 + 2] Process.[25] Study of the Stereocontrol. The cascade was then extended to the addition of radical centers located α to an ester group (i.e., **IV**, Scheme 2). Addition of these ambiphilic radicals[26] onto olefins is a useful process which produces a new radical that can be trapped intra- or intermolecularly in a stereocontrolled manner. Such additions were shown to be particularly efficient on electron-rich allylsilanes. The resulting β-silyl radical intermediate can then react further

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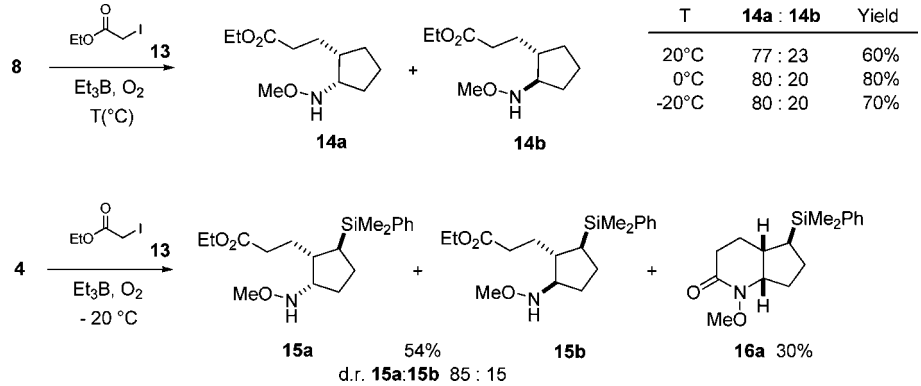
SCHEME 4. Preliminary Studies on the Radical Additions of α-Iodoester 13 to Enoximes 4 and 8

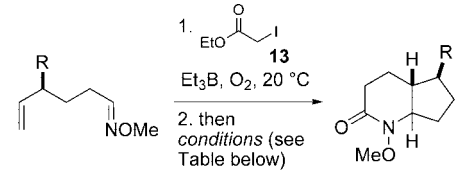


with azides, xanthates, and bromoamides, with a high level of stereocontrol.[13,27] Although 5-*exo*- and 6-*exo-trig* cyclizations onto oximes are known to be fast processes,[19] halogen atom transfer may however compete to provide the corresponding β-halosilanes.[28]These species are known to β-eliminate readily even at low temperatures to produce an olefin.[13a,29] Aware of this potential drawback, we added α-iodoester **13** to nonsilylated enoxime **8** in the presence of Et_3B as an initiator (Scheme 4). We were pleased to observe that as with thiyl radicals, the addition proceeded smoothly and was followed by the cyclization to provide cyclopentanes **14a**,**b** in good yields and modest selectivities in the favor of the *cis*-isomer. In contrast to the above studies, lowering the temperature had little effect on the yield and stereocontrol. In none of these experiments have we observed the formation of the piperidinone skeleton. The cascade process was then applied to enoxime **4** which provided a mixture of *cis*- and *trans*-cyclopentanes **15a**,**b** as well as the expected [2 + 2 + 2] product **16a** as a single diastereomer (stereochemistry as shown), resulting from a spontaneous lactamization which occurred only with the *cis*-cyclopentane isomer **15a**. These preliminary results indicated that the 5-*exo-trig* cyclization was faster than the iodine atom transfer since no olefin formation was observed.

The process thus occurred with a very satisfying 91:9 stereoselectivity. As before with sulfur models, the *trans,cis* stereoisomer **15a** (and **16a**) was formed predominantly. In order to obtain the exclusive formation of **16a**, the lactamization of amino esters **14a**,**b** and **15a**,**b** was then studied using various conditions, including acidic (TFA), basic (K_2CO_3, EtOH), as well as Weinreb conditions (Me_3Al) (Scheme 5).[30] Treatment with TFA led to the desired piperidinones in good yield and excellent stereocontrol. Et_3N in ethanol at reflux, and also Me_3Al in toluene at 100 °C, led to the desired piperidinones **16a**,**b** and **17a**,**b**, albeit in lower yield.

In our quest for a more straightforward "one-pot" [2 + 2 + 2] process, we finally found that exchanging a phenyl ester for the ethyl ester led directly to the piperidinone. Further treatments

SCHEME 5. Two-Pot Radical−Cascade−Lactamization Process



4 R = $SiMe_2Ph$ **16a-b** R = $SiMe_2Ph$
8 R = H **17a-b** R = H

oxime	*conditions*	*cis* : *trans* **a** : **b**	yield
4	TFA, PhH, 85 °C	95 : 5	70%
8	Et_3N, EtOH, reflux	80 : 20	53-56%
4	Me_3Al, $PhCH_3$, 100 °C	95 : 5	57%

with acidic, basic, or organometallic conditions described above were no longer required. For instance, radical addition of iodoester **18**[31] onto enoxime **8**, followed by 5-*exo-trig* cyclization and lactamization, occurred smoothly to provide a 76:24 mixture of *cis*- and *trans*-piperidinones **17a**,**b** in 69% yield (Table 2, entry 1). After some optimizations, the one-pot process was extended to the cyclization of enoximes having allylic stereogenic centers. The results are summarized in Table 2. The best yields and diastereoselectivities were observed with enoximes having an allylsilane moiety (Table 2, entries 2−5). With these precursors, the *trans*,*cis*-isomer was obtained predominantly with only a small amount of *trans*,*trans*-isomer being observed in one case (entry 3). The presence of a β-substituent (R′) brought little change in the level of stereocontrol (entries 3−5). Similarly, when *tert*-butyl precursor **10** was treated under the optimized conditions, the piperidinone was formed with excellent stereocontrol in favor of the *trans,cis* stereoisomer **23a**, although the yield of **23a** was modest (entry 7). In contrast, application of the radical cascade to precursor **9** (R = Me) led to a 85:13:2 mixture of three stereoisomers (out of four possible diastereomers) as shown by the ^{1}H NMR of the crude reaction mixture. The relative configuration of the two major products was assumed to be respectively *trans,cis* and *trans,trans*, in agreement with that of the *tert*-butyl analogue which is assumed to lead to a similar stereochemical outcome.

(27) (a) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2002**, *4*, 4257–4260. (b) Briggs, M. E.; Zard, S. Z. *Synlett* **2005**, 334–336. (c) Chabaud, L.; Landais, Y.; Renaud, P.; Robert, F.; Castet, F.; Lucarini, M.; Schenk, K. *Chem.—Eur. J.* **2008**, *14*, 2744–2756.

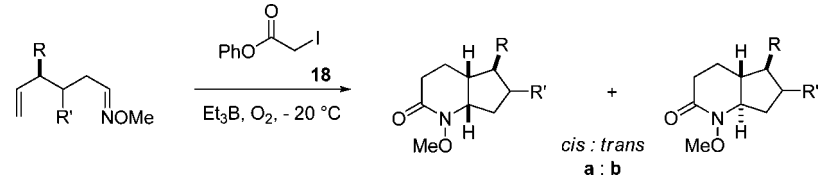
(28) Rate constants for 5-*exo-trig* cyclizations onto oximes and iodine atom transfer from α-iodoacetate have been estimated: $k \sim 3.\ 1^7$ and $k \sim 1^7$ M s^{-1}, respectively.

(29) (a) Guindon, Y.; Guérin, B.; Chabot, C. C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1996**, *118*, 12528–12535. (b) Masterson, D. S.; Porter, N. D. *Org. Lett.* **2002**, *4*, 4253–4256. (c) Chabaud, L.; Landais, Y. *Tetrahedron Lett.* **2003**, *44*, 6995–6998.

(30) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1988**, *50*, 492–495.

(31) Phenyl iodoacetate was prepared following a two-step sequence, including the reaction of phenol with the α-chloroacetyl chloride followed by the exchange of chlorine for iodine using NaI in acetone (see the Supporting Information).

TABLE 2. [2 + 2 + 2]-Radical-Ionic Cascade Involving Enoximes



entry	oxime	R	R′	Et_3B (equiv)	product	dr (**a**:**b**)[a]	yield[c] (%)
1	**8**	H	H	2	**17a**,**b**	76:24	69
2	**4**	$SiMe_2Ph$	H	3	**16a**,**b**	>95:5	76
3	**5**	$SiMe_2Ph$	CO_2Me	3	**19a**,**b**	>90:10	61
4	**6**	$SiMe_2Ph$	OAc	3	**20a**,**b**	>95:5	78
5	**7**	$SiMe_2Ph$	Me	3	**21a**,**b**	>95:5	85
6	**9**	Me	H	6	**22a**,**c**	85:13:2[b]	51
7	**10**	*t*-Bu	H	6	**23a**,**b**	>95:5	47

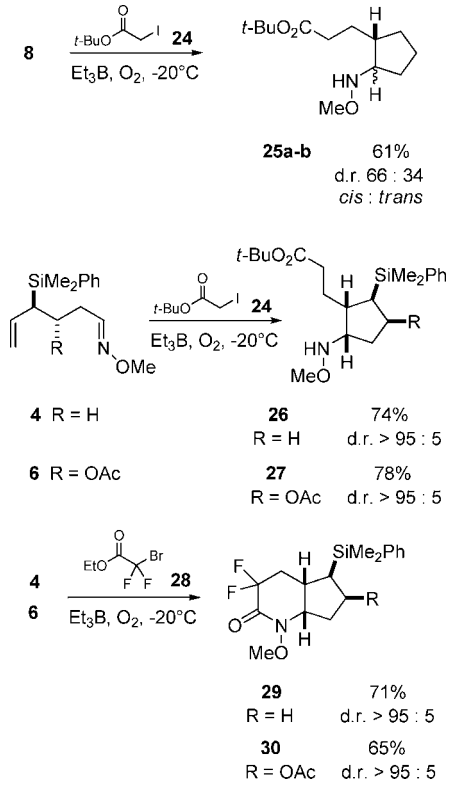
[a] Estimated ratio through ^1H NMR of the crude reaction mixture. [b] Ratio estimated through GC. [c] Isolated yield of both isomers.

The poor efficiency of radical additions[32] onto olefins bearing an alkyl group on the allylic stereogenic center was already noticed in related sulfonyl process onto 1,6-dienes.[12a−d] Such a result further demonstrates the beneficial effect of an allylic silicon group on the efficiency of the addition step, which can be attributed to the σ-donating effect of this silicon substituent (polar effect, vide infra).[23]

The effect of the structure of the α-iodo ester component was further studied. As anticipated, the addition of α-iodo *tert*-butyl ester **24** did not affect the stereochemical course of the process; it, however, considerably slowed down the lactamization step, such that cyclopentanes **25a**,**b**, **26**, and **27** were now isolated without traces of the corresponding piperidinones (Scheme 6). As above, excellent diastereoselectivities were observed with silylated precursors **4** and **6** and a lower *cis/trans* ratio with simpler model **8**. Functionalized α-bromo-α,α-difluoroester **28**[33] was also tested and led to fluorinated piperidinones **29** and **30** in yields and selectivities similar to those obtained previously. Attempts to use α-bromo esters or α-iodolactone however met with little success. Weinreb α-iodoamides behave similarly to the corresponding ethyl esters, leading to mixtures of the corresponding aminoamides and piperidinones and were not studied further. As a summary, the addition-5-*exo-trig* cyclization sequence using various esters and ene−aldoxime precursors can be performed with good chemical efficiency and excellent level of stereoinduction, provided that a silicon group is present at the allylic position of the ene−aldoxime component. In addition, we have also demonstrated that the final lactamization can be favored or disfavored simply by tuning the structure of the α-iodoester substituent.

Trans,cis relative configurations were firmly established from X-ray diffraction studies on cyclopentane **12a** and from NOEs measured on silylated piperidinone **20a** (see the Supporting Information). From these and previous observations from 5-*exo-trig* processes carried out on 1,6-dienes,[12a−d] a transition-state model was proposed to rationalize the stereochemical outcome resulting from the cyclization step. Ab initio calculations on 5-*exo-trig* cyclizations performed by Houk and Schiesser[34] established that such cyclizations occur through a chairlike transition state, in which steric effects and torsional strain are

SCHEME 6. Study on the Effect of the Nature of the α-Iodoester



minimized. This model was recently revisited in sulfonyl radical mediated 5-*exo-trig* processes with the implementation of a bulky silicon group on the carbon chain.[12d] Application of this model to the enoxime case (i.e., **A**, Scheme 7) leads to a transition state where the silicon group occupies a pseudoequatorial position in order to minimize steric interactions with neighboring substituents. Interestingly, such a model also implies a quasi linear arrangement of the electron-rich C2−Si bond and the incipient C1−C5 bond, reminiscent of the well-known β-silicon effect,[35] which likely stabilizes further this transition

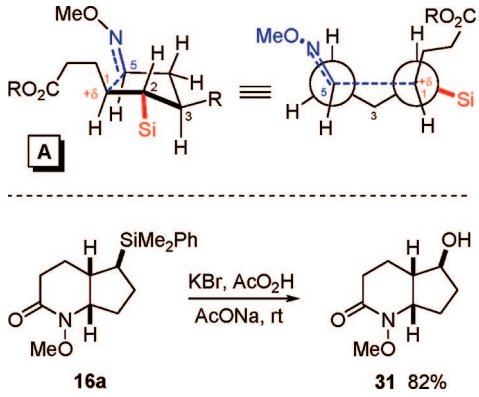
(32) Larger amounts of Et_3B (up to 6 equiv) were always required to allow the reaction to reach completion.

(33) Moreno, B.; Quehen, C.; Rose-Hélène, M.; Leclerc, E.; Quirion, J. C. *Org. Lett.* **2007**, *9*, 2477–2480.

(34) (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925–3941. (b) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959–974. (c) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373–376. (d) Beckwith, A. L. J.; Zimmerman, J. *J. Org. Chem.* **1991**, *56*, 5791–5796.

(35) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677–2689, and references therein.

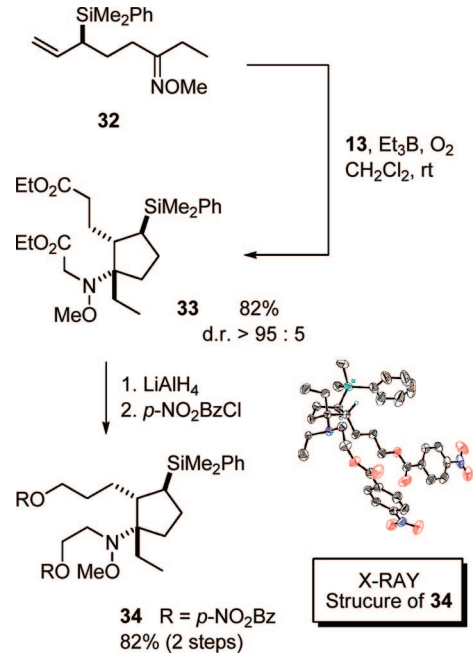
SCHEME 7. Transition-State Model for the 5-*Exo-Trig* Cyclization and Oxidation of the $PhMe_2Si$ Group



state. As demonstrated in the studies above, the silicon group not only activates the olefin toward the addition of electrophilic radicals but also locks the conformation at the transition state, allowing high levels of 1,2- and 1,3-stereocontrol. A similar behavior is observed with the *t*-Bu group (i.e., **10**) which in turn lacks the polar component of the silicon group, resulting in a much less efficient addition step (entry 7, Table 2). It was finally shown that the silicon group could be converted into the corresponding hydroxyl, using the buffered Fleming−Tamao oxidation,[36] with retention of configuration, thus providing the alcohol **31** in excellent yield.

***5-Exo-Trig* Cyclization onto Ketoximes. A Recombination Process.** The successful approach to piperidinones described above prompted us to extend this strategy to ketoximes analogues (Scheme 2, R′ = alkyl, aryl). Radical addition followed by a 5-*exo-trig* cyclization onto a ketoxime function would provide a cyclopentane ring having a quaternary center and a carbon chain that may possess functional groups allowing further elaboration.[37] Such an approach would be well suited to access the tricyclic skeleton of alkaloids such as lepadiformine **3** and its congeners (Scheme 1). Our investigations started with allylsilane−ketoxime **32** (see Supporting Information for preparation) (Scheme 8). When submitted to α-iodoester **13** (2 equiv) and triethylborane, ketoxime **32** did not however furnish the expected piperidinone. We instead isolated a material incorporating two ester fragments, assigned as cyclopentane **33**, which was formed as a single stereoisomer. Although all analytical elements spoke in favor of cyclopentane **33** (^{1}H, ^{13}CNMR, COSY, HMQC, and HRMS), its structure was unambiguously proven via X-ray diffraction studies conducted on diester **34**. These studies allowed us to establish the relative stereochemistry of cyclopentane **33** as being *trans*,*cis*, which corroborates the results obtained in the aldoxime series. The cyclization likely proceeds through a conformation at the transition state closely resembling to **A** (Scheme 7), the ethyl group inducing little steric effects. This unexpected result is noteworthy as it demonstrates that the cyclization onto the ketoxime is still favored relative to the iodine atom transfer. The same reaction carried out using the corresponding xanthate (Scheme 2) led to the same product albeit in much lower yield (8%). Interestingly, when only one equivalent of **13** was employed, cyclopentane **33** was obtained

SCHEME 8. Radical Addition−5-*Exo-Trig* Cyclization on Ketoxime 32



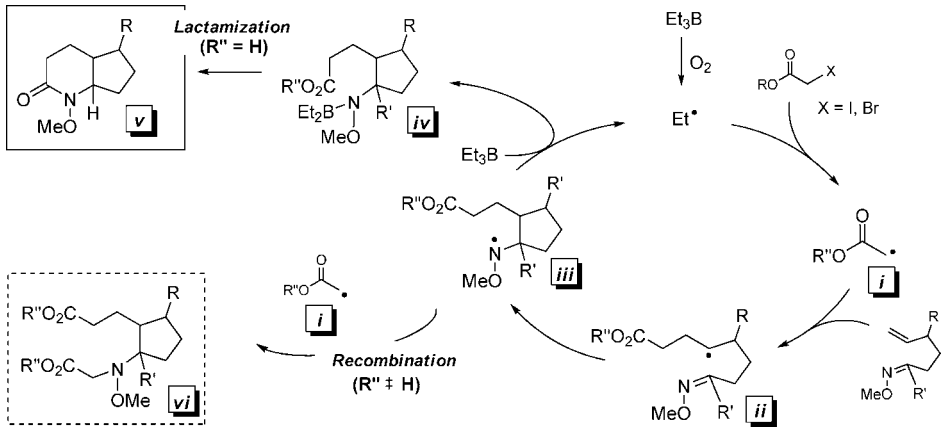
in 45% yield along with unreacted **32** (35% recovery), indicating that lactamization was not competitive with the formation of the diester **33**.

In an effort to rationalize the [2 + 2 + 2] process as well as the unexpected formation of diester **33**, we proposed the mechanistic scheme below (Scheme 9). The electrophilic radical species ***i*** is known to be formed through abstraction of iodine by an ethyl radical issued from the reaction of Et_3B with oxygen. ***i*** then regioselectively adds on the less substituted end of the electron-rich olefinic system to produce nucleophilic radical ***ii*** (β to silicon).[24] The oxime functionality in ***ii*** is appropriately located for the radical species to cyclize in a 5-*exo-trig* fashion, providing alkoxyaminyl radical intermediate ***iii***. This nitrogen centered radical can then react with Et_3B and form via a polar crossover process,[20] amido−borane complex ***iv*** which is able to lactamize and produce piperidinone ***v***. While this pathway is highly efficient with aldoximes (R′ = H), it is not observed in the case of ketoximes. Among possible hypotheses that could be envisioned to rationalize this unexpected behavior, we reasoned that diester ***vi*** (e.g., **33**) could result either from a S_N2 displacement of iodide **13** by amido-borane intermediate ***iv*** (R′ ≠ H) or through a direct radical recombination of alkoxyaminyl radical ***iii*** (R′ ≠ H) and radical ***i***. Both pathways were thus investigated. For instance, the radical reaction was carried out as described above on **32**, except that water was used as a solvent. This led to the unique formation of diester **33**. Similar results were obtained when additives such as AcOH (1−5 equiv) were employed. Strikingly, the reaction can even be conducted in 1 N HCl or in concd H_2SO_4 and still leads to the exclusive formation of **33** (albeit in lower chemical efficiency). Electrophiles such as $(Boc)_2O$ and trifluoroacetic anhydride were also tested to trap the putative amidoborane ***iv***, but **33** was invariably produced as a unique product. These experiments clearly rule out the formation of the C−N bond and the incorporation of the second ester fragment through an ionic pathway. Therefore, we next examined the alternative radical recombination pathway. We envisioned that significant steric hindrance around the nitrogen atom might prevent the approach of Et_3B and thus

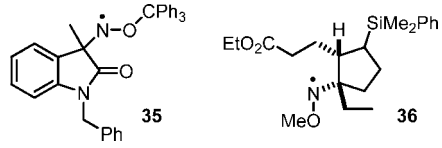
(36) (a) Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1–64. (b) Tamao, K. In *Advances in Silicon Chemistry*; JAI Press Inc.: New York, 1996; Vol. 1, pp 1−62. (c) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599–7662.

(37) For a recent study on a free-radical addition−6-*exo-trig* cascade, see: Fernandez-Gonzalez, M.; Alonso, R. *J. Org. Chem.* **2006**, *71*, 6767–6775.

SCHEME 9. Mechanistic Proposal for the [2 + 2 + 2] Radical Cascade



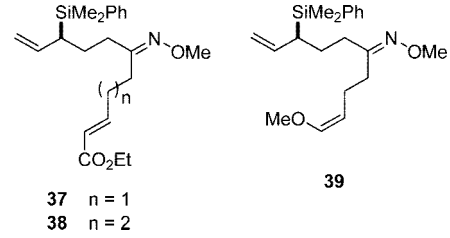
SCHEME 10. Persistent Alkoxyaminyl Radicals



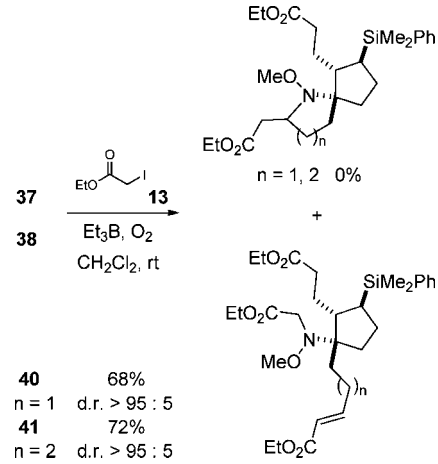
prohibit the formation of amido-borane complex ***iv***. Precedents from the literature effectively reveal that alkoxyaminyl radicals, such as **35**, are persistent due to steric shielding (Scheme 10).[38] In our case, intermediate radical **36** may fit into this category and therefore possess a long enough lifetime to recombine with an excess of radical precursor ***i*** arising from α-iodoester **13**. Several experiments were designed to reduce the alkoxyaminyl radical intermediate ***iii*** (R′ ≠ H) under free-radical conditions. For instance, addition of ethyl xanthate in isopropanol as both a solvent and a reducing agent, according to Zard's procedure,[39] led to **33** in low yield (8%) along with recovered starting material (78%). No trace of the desired reduced product was observed. The use of Roberts's polarity-reversal catalysis[40] (Ph_3SiH, $HSCH_2CO_2Et$ (cat.), $BrCH_2CO_2Et$) led in turn to a complex mixture of products in which the desired product was absent. Finally, substitution of Et_3B for indium[41] in a MeOH−-H_2O mixture led to recovered allylsilane **32** and ethyl acetate resulting from complete reduction of **13**.[42]

In parallel, we envisaged being able to trap the alkoxyaminyl radical (i.e., **iii**) in an intramolecular fashion through the introduction of an olefinic appendage. Recent studies by Jaramillo-Gomez et al.[43] effectively showed that a 5-*exo-trig* cyclization onto a ketoxime, followed by a second 5-*exo-trig* addition of an alkoxyaminyl radical onto an unsaturated Michael acceptor, was feasible, leading to a good yield of the desired bicyclic system. Three different precursors **37**, **38**, and **39** were thus designed (Scheme 11), possessing electron-poor and

SCHEME 11. Unsaturated Ketoximes 37−39



SCHEME 12. Radical Cascade and Recombination Step of Ketoximes 37 and 38

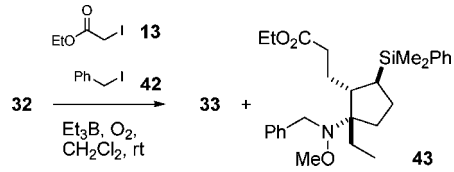


electron-rich olefins that could trap the alkoxyaminyl radical in a 5-*exo-trig* and 6-*exo-trig* fashion, respectively (see the Supporting Information for preparation).

Ketoximes **37**−**39** were then submitted to the radical addition of α-iodoester **13**. Under the conditions described above, **37**−**38** led to the corresponding recombination products **40** and **41** after radical addition and 5-*exo-trig* cyclizations. Unfortunately, no traces of the desired spiro-bicylic systems were detected. Both **40** and **41** were isolated as single diastereomers with the stereochemistry as shown (Scheme 12). In sharp contrast, precursor **39** led to a complex mixture where none of the expected products (recombination or cyclized) could be identified, presumably due to the instability of the enol ether functionality under the radical conditions. This last series of experiments demonstrates that the generation of the N−CH_2CO_2Et bond is faster than the intramolecular addition of the intermediate alkoxyaminyl radical on the Michael acceptor appendage.

(38) Bella, A. F.; Slawin, A. M. Z.; Walton, J. C. *J. Org. Chem.* **2004**, *69*, 5926–5933.
(39) Boiteau, L.; Boivin, J.; Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1998**, *37*, 1128–1131.
(40) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25–35.
(41) (a) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454–5. (b) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* **2004**, *60*, 4227–4235. (c) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131–134. (d) Bernardi, L.; Cere, V.; Femoni, C.; Pollicino, S.; Ricci, A. *J. Org. Chem.* **2003**, *68*, 3348–3351. (e) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955–977.
(42) Ranu, B. C.; Dutta, P.; Sarkar, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1139–1140.
(43) Jaramillo-Gomez, L. M.; Loaiza, A. E.; Martin, J.; Rios, L. A.; Wang, P. G. *Tetrahedron Lett.* **2006**, *47*, 3909–3912.

TABLE 3. Radical Cascade and Recombination Step



entry	**13** (equiv)	**42** (equiv)	**32**:**33**:**43**[a]
1	0	4	–[b]
2	2.5	2.5	50:28:22[c]
3	2.5	2.5	5:46:49[d]
4	2.5	2.5	5:38:57[e]
5	2.5	1.5	25:47:28[e]
6	1.5	4	30:14:56[e]
7	1.5	10	80:1:19[e]

[a] Estimated ratio through ^{1}H NMR of the crude reaction mixture. [b] **13** and **42** in solution in CH_2Cl_2, Et_3B (2 equiv) and air are successively added. [c] **42** was added slowly through a syringe pump. [d] Et_3B was added slowly through a syringe pump. [e] **13** and **42** were added slowly through a syringe pump.

In order to firmly establish the occurrence of a radical recombination pathway and propose a useful alternative to this process, it was envisioned that introduction in the medium of a second radical source might enable crossover recombination. These radicals would, however, be required to (1) be unreactive toward the olefin fragment (polar effect), (2) possess a sufficient lifetime for recombination with **36**, and (3) be easily generated from ethyl radicals arising from Et_3B. Benzyl radical was thus elected as a good candidate. Hence, recombination of benzyl radical and **36** would provide the corresponding benzylamine which would be a versatile intermediate en route to the desired piperidinones. The radical reaction was thus conducted in the presence of benzyl iodide. Results are summarized in Table 3. We first performed a control experiment and showed that benzyl radicals alone did not add onto the olefin (Table 3, entry 1). In the presence of various amounts of benzyl iodide **42**, benzyl-recombined cyclopentane **43** was effectively produced. When both radical precursors were introduced in equimolar amounts in the medium, **33** and **43** were generated in a 1:1 ratio (entry 2). Better yields of the benzyl derivative **43** were obtained through the syringe pump introduction of both **13** and **42** (entries 4−7). In line with this observation, larger amounts of benzyl amine **43** were formed using 4−10 equiv of benzyl iodide **42** (entries 6 and 7). Recombination of radicals being a fast process, the competing radical recombination between **36** and ***i*** and between **36** and benzyl radicals is probably a direct reflection of the relative amounts of radical ***i*** and benzyl radical present in the medium. The linear correlation between **13/42** and **33/43** ratio (Table 3) argues in this direction. The ionic pathway was finally excluded on the basis of a last experiment where highly nucleophilic secondary alkoxyamine **27** prepared above was treated with an excess of benzyl iodide **42** (2.8 equiv) in CD_2Cl_2 at room temperature in the absence of a base. Under these conditions, which closely match those of the radical process depicted in Table 3, no trace of the corresponding benzylamine could be detected even after 20 h (see the Supporting Information), further discounting a S_N2 process. Taken altogether, these series of experiments clearly suggest that recombination of radical species **36** and ***i*** is the likely pathway leading to diester **33**. Interestingly, benzyl amine **43** can be regarded as the result of a three-component one-pot radical addition-5-*exo-trig* cyclization-recombination process. This radical cascade is noteworthy and might be considered as a valuable new multicomponent reaction.[44] It implies the generation of two C−C and one C−N bonds and relies on the interruption of the [2 + 2 + 2]-process by an unexpected recombination step.

Conclusion

We described along these lines a stereocontrolled access to five-membered ring fused piperidinones through a formal [2 + 2 + 2] process involving a cascade of radical steps, followed by a radical polar crossover process and concluded by an ionic lactamization. Excellent yields and stereoselectivities were generally observed starting from enoximes bearing a chiral allylsilane moiety, thus demonstrating the beneficial role of an allylic silicon group regarding the chemical reactivity and the stereocontrol (1,2 and 1,3). Extension of the cascade to the radical addition onto ketoximes was not followed by lactamization but instead by the recombination of the resulting alkoxyaminyl radical with the radical species issued from the starting α-iodoester. We showed that such a recombination could be used to devise a three-component process where two different radicals are added on the enoxime precursor, providing a cyclopentane bearing three contiguous stereocenters and a benzylamine appendage. Further development of this type of multicomponent radical reaction is currently actively being pursued in our laboratory.

Experimental Section

Acetic Acid 2-(Dimethylphenylsilanyl)-4-methoxyamino-3-phenylsulfanylmethylcyclopentyl Ester (12a). To a solution of allylsilane oxime **6** (100 mg, 0.31 mmol, 1 equiv) in degassed toluene (3 mL) was added thiophenol (62 μL, 0.62 mmol, 2 equiv). The solution was thermostated at 25 °C, and the reaction mixture was irradiated with a sun lamp for 6 h. TLC then indicated complete consumption of the starting material. Solvent was then removed in vacuo. Flash chromatography (silica gel, 80:20 → 75:25 petroleum pther/EtOAc) afforded the title compound **12a** as a yellow solid as a 88:12 mixture with its diastereomer **12b** (125 mg, 95% combined yield): IR (neat, NaCl) ν_{max} (cm^{-1}) 2938, 1743, 1584, 1427, 1372, 1247, 1112, 1023; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47−7.51 (m, 2H), 7.35−7.35 (m, 3H), 7.11−7.24 (m, 5H), 5.95 (bs, 1H), 5.41 (dt, J = 3.0, 6.4 Hz, 1H), 3.68 (q, J = 6.4 Hz, 1H), 3.50 (s, 3H), 2.85 (dd, J = 4.5, 12.4 Hz, 1H), 2.68 (dd, J = 10.6, 12.4 Hz, 1H), 2.40−2.52 (m, 1H), 2.20−2.3 (m, 1H), 1.91 (s, 3H), 1.73−1.87 (m, 2H), 0.33 (s, 3H), 0.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.2, 138.6, 136.3, 133.6, 129.1, 128.9, 127.9, 126.0, 78.6, 62.3, 61.2, 43.0, 38.8, 36.1, 34.0, 21.2, −2.6, −3.1; HRMS (LSIMS) calcd for $C_{23}H_{32}NO_3SSi$ [M + H$^+$] 430.1872, found 430.1860.

General Procedure for "One Pot" Radical Addition−Ionic Lactamization Processes. To a solution of oxime (1 equiv) in CH_2Cl_2 (0.1 M) (not degassed) under an N_2 atmosphere was added the desired α-iodoester (see text for number of equivalents). The resulting mixture was cooled to the indicated temperature (generally −20 °C), and Et_3B (1.0 m in hexane, see text for number of equivalents) was added. A balloon filled with O_2 was then adapted above the flask, and the mixture was stirred at the same temperature until TLC indicated complete consumption of the starting oxime. In the case of nonsilylated oxime, completion of the reaction often required additional Et_3B injections (via portions of 2 equiv directly in the solution to avoid premature reaction with the O_2 atmosphere, 1.0 M in hexane, see text for total number of equivalents) every

(44) (a) *Multicomponent Reactions*; Bienaymé, H., Zhu, J., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Stuttgart, 2005. (b) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321–3329. (c) Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662–12663.

3 h until no starting material could be identified by TLC. Volatile materials were then removed in vacuo, and the resulting crude oil was purified by flash chromatography (silica gel).

5-(Dimethylphenylsilanyl)-1-methoxy-6-methyloctahydro[1]pyridin-2-one (16a). Prepared according to the general procedure described above from allylsilane oxime **4** (0.100 g, 0.38 mmol, 1 equiv), phenyl iodoacetate **18** (0.199 g, 0.76 mmol, 2 equiv), and triethylborane (1.0 M in hexane 0.76 mL, 0.76 mmol, 2 equiv) in CH_2Cl_2 (3.8 mL) at −20 °C. Flash chromatography (silica gel, 80:20 CH_2Cl_2/AcOEt) afforded title compound **16a** as a yellow oil (0.087 g, 76%): R_f = 0.25 (silica gel, 80:20 CH_2Cl_2/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2952, 2867, 1673, 1427, 1348, 1249, 1113, 835, 701; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.46−7.51 (m, 2H), 7.33−7.38 (m, 3H), 3.75−3.80 (m, 4H), 1.08−2.44 (m, 8H), 0.30 (s, 3H), 0.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 167.6, 137.5, 133.7, 129.3, 127.9, 63.9, 61.6, 40.0, 32.7, 31.4, 29.6, 26.0, 25.7, −4.5, −4.9; HRMS (LSIMS) calcd for $C_{17}H_{24}NOSi$ [M + H^+] 304.1733, found 304.1736.

1-Methoxyoctahydro[1]pyridin-2-one (17a,b). Prepared according to the general procedure described above from oxime **8** (0.100 g, 0.79 mmol, 1 equiv), phenyl iodoacetate **18** (0.414 g, 1.6 mmol, 2 equiv), and triethylborane (1.0 M in hexane, 1.6 mL, 1.6 mmol, 2 equiv) in CH_2Cl_2 (7.9 mL) at −20 °C. Flash chromatography (silica gel, 85:15 petroleum ether/EtOAc) afforded minor diastereoisomer **17b** (0.022 g, 16%) and major diastereomer **17a** (0.070 g, 52%). Major diastereomer **17a**: R_f = 0.17 (silica gel, 60:40 CH_2Cl_2/EtOAc); IR (neat) ν_{max} (cm^{-1}) 3460 (bs), 2940, 1652, 1455, 1414, 1347, 1192, 1081, 974; ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm) 3.97 (q, J = 5.7 Hz, 1H), 3.77 (s, 3H), 2.29−2.48 (m, 3H), 1.40−2.04 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 167.4, 62.8, 61.5, 38.0, 31.7, 31.2, 29.8, 24.0, 23.0; HRMS (EI) calcd for $C_9H_{15}NO_2$ [M^+] 169.1103, found 169.1105. Minor diastereomer **17b**: R_f = 0.35 (silica gel, 60:40 CH_2Cl_2/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2939, 1660, 1460, 1351, 1200, 1044, 991; ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm) 3.75 (s, 3H), 3.26 (dt, J = 6.7, 11.0 Hz, 1H), 2.50−2.56 (m, 2H), 2.06−2.16 (m, 1H), 1.23−1.95 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.0, 67.0, 62.5, 44.8, 33.9, 29.2, 27.4, 25.6, 21.0; HRMS (EI) calcd for $C_9H_{15}NO_2$ [M^+] 169.1103, found 169.1105.

5-(Dimethylphenylsilanyl)-1-methoxy-2-oxooctahydro[1]pyridin-6-carboxylic Acid Methyl Ester (19a). Prepared according to the general procedure described above from oxime **5** (0.029 g, 0.09 mmol, 1 equiv), phenyl iodoacetate **18** (0.047 g, 0.18 mmol, 2 equiv), and triethylborane (1.0 M in hexane, 0.18 mL, 0.18 mmol, 2 equiv) in CH_2Cl_2 (1.8 mL) at −20 °C. Flash chromatography (silica gel, 90:10 → 60:40 CH_2Cl_2/EtOAc) yielded title compound **19a** (0.020 g, 61%) as a colorless oil: R_f = 0.39 (silica gel, 70:30 CH_2Cl_2/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2956, 1723, 1668, 1428, 1113; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.48−7.51 (m, 2H), 7.35−7.39 (m, 3H), 3.65−3.73 (m, 1H), 3.71 (s, 3H), 3.56 (s, 3H), 2.67 (dt, J = 6.8, 10.6 Hz, 1H), 2.19−2.47 (m, 3H), 2.02 (q, J = 10.2 Hz, 1H), 1.54−1.71 (m, 4H), 0.32 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 175.5, 167.5, 136.4, 133.9, 129.6, 128.1, 63.3, 62.0, 52.0, 44.1, 40.3, 37.2, 33.5, 31.9, 26.3, −4.5, −4.9; HRMS (EI) calcd for $C_{19}H_{27}NO_4Si$ [M^+] 361.1709, found 361.1701.

Acetic Acid 5-(Dimethylphenylsilanyl)-1-methoxy-2-oxooctahydro[1]pyridin-6-yl Ester (20a). Prepared according to the general method described above from oxime **6** (0.120 g, 0.37 mmol, 1 equiv), phenyl iodoacetate **18** (0.19 g, 0.74 mmol), and triethylborane (1.0 M in hexane, 0.74 mL, 0.74 mmol) in CH_2Cl_2 (3.7 mL). Flash chromatography (silica gel, 80:20 → 60:40 CH_2Cl_2/EtOAc) afforded title compound **20a** as a yellow oil (0.105 g, 78%): R_f = 0.36 (silica gel, 70:30 CH_2Cl_2/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2936, 1736, 1672, 1427, 1372, 1234, 1112; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47−7.51 (m, 2H), 7.35−7.36 (m, 3H), 5.38 (t, J = 4.9 Hz, 1H), 4.13 (q, J = 6.4 Hz, 1H), 3.74 (s, 3H), 2.50−2.61 (m, 1H), 2.21−2.34 (m, 3H), 2.01−2.28 (m, 1H), 1.95 (s, 3H), 1.51−1.55 (m, 3H), 0.39 (s, 3H), 0.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.1, 167.7, 137.8, 133.6, 129.5, 128.1, 78.0, 62.0, 61.9, 40.2, 39.7, 36.6, 31.4, 25.4, 21.3, −3.0, −3.2; HRMS (LSIMS) calcd for $C_{19}H_{27}O_4NSiNa$ [M + Na^+] 384.1607, found 384.1602.

5-(Dimethylphenylsilanyl)-1-methoxy-6-methyloctahydro[1]pyridin-2-one (21a). Prepared according to the general procedure described above from oxime **7** (0.042 g, 0.15 mmol, 1 equiv), phenyl iodocetate **18** (0.079 g, 0.30 mmol, 2 equiv), and triethylborane (1.0 M in hexane, 0.30 mL, 0.30 mmol, 2 equiv) in CH_2Cl_2 (1.5 mL) at −20 °C. Flash chromatography (silica gel, 80:20 → 75:25 CH_2Cl_2/EtOAc) yielded lactam **21a** (0.041 g, 85%) as a colorless oil: R_f = 0.27 (silica gel, 75:25 CH_2Cl_2/EtOAc); IR (neat) ν_{max} (cm^{-1}) 3464, 2956, 1668, 1428, 1250, 1112, 811; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.49−7.52 (m, 2H), 7.33−7.35 (m, 3H), 4.10 (q, J = 7.2 Hz, 1H), 3.73 (s, 3H), 2.13−2.55 (m, 4H), 1.75−1.94 (m, 2H), 1.51−1.62 (m, 1H), 1.30−1.41 (m, 2H), 0.92 (d, J = 7.2 Hz, 3H), 0.35−0.36 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 168.4, 138.7, 133.5, 129.0, 127.8, 62.2, 61.5, 41.5, 39.1, 36.1, 35.0, 30.8, 25.0, 19.3, −2.6, −2.9; MS (FAB$^+$) m/z calcd for $C_{18}H_{27}NO_2Si$ [M + Na^+] 340.17, found 340.18, calcd for $C_{18}H_{27}NO_2Si$ [M + H^+] 318.19, found 318.20. HRMS (EI) calcd for $C_{18}H_{27}NO_2Si$ [M + H^+] 317.1811, found 317.1808.

1-Methoxy-5-methyloctahydro[1]pyridin-2-one. Major Diastereomer (22a). Prepared according to the general procedure described above from oxime **9** (0.120 g, 0.85 mmol, 1 equiv), phenyl iodoacetate **18** (0.442 g, 1.68 mmol, 2 equiv), and triethylborane (1.0 m in hexane, 1.7 mL, 1.7 mmol, 2 equiv) in CH_2Cl_2 (3.8 mL) at −20 °C. Additional triethylborane (1.0 m in hexane, 3.4 mL, 3.4 mmol, 4 equiv) was required to completely consume all starting materials. Flash chromatography (silica gel, 90:10 → 80:20 CH_2Cl_2/EtOAc) afforded major diastereomer **22a** (0.068 g, 44%) and a 9:1 mixture of 2 other inseparable diastereomers **22b** and **22c** (0.012 g, 8%). Major diastereomer **22a**: R_f = 0.75 (silica gel, 80:20 CH_2Cl_2/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2952, 1652, 1456, 1418, 1349, 1072, 976, 920; ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm) 4.04 (q, J = 7.0 Hz, 1H), 3.75 (s, 3H), 2.32−2.43 (m, 2H), 2.04−2.19 (m, 1H), 1.59−1.98 (m, 5H), 1.08−1.27 (m, 2H), 1.01 (d, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 167.7, 62.5, 61.6, 46.1, 37.5, 32.5, 31.8, 31.1, 22.7, 19.8; MS (EI) m/z calcd for $C_{10}H_{17}NO_2$ [M^+] 183.2, found 183.2; HRMS (EI) calcd for $C_{10}H_{17}NO_2$ [M^+] 183.1259, found 183.1239. Minor diastereoisomers **22b** and **22c** were isolated as a mixture of two diastereoisomers in a 90:10 ratio as determined by GC−MS analysis. Relative stereochemistry was not determined: R_f = 0.39 (silica gel, 90:10 CH_2Cl_2/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2952, 1689, 1462, 1374, 1333, 1203, 1109, 1045; ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm) 3.59−3.80 (s, 3H), 3.30−3.43 (m, 1H), 2.48−2.62 (m, 2H), 1.85−2.15 (m, 3H), 1.59−1.80 (m, 2H), 1.35−1.54 (m, 3H), 1.03−1.05 (m, 0.9 × 3H), 0.86−0.89 (m, 0.1 × 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) (only diastereomer **22b** signals are reported) δ (ppm) 171.2, 66.8, 63.0, 51.8, 35.7, 34.1, 30.7, 28.1, 24.3, 19.0; MS (EI) m/z calcd for $C_{10}H_{17}NO_2$ [M^+] 183.3, found 183.2.

5-*tert*-Butyl-1-methoxyoctahydro[1]pyridin-2-one (23a). Prepared according to the general procedure described above from oxime **10** (0.098 g, 0.53 mmol, 1 equiv), phenyl iodocetate **18** (0.28 g, 1.09 mmol, 2 equiv), and triethylborane (1.0 m in hexane, 1.09 mL, 1.09 mmol, 2 equiv) in CH_2Cl_2 (3.8 mL) at −20 °C. Additional triethylborane (1.0 M in hexane, 2.2 mL, 2.2 mmol, 4 equiv) was required to completely consume all starting materials. Flash chromatography (silica gel, 80:20 → 65:35 CH_2Cl_2/EtOAc) yielded the lactam **23a** (0.055 g, 47%) as a colorless oil: R_f = 0.32 (silica gel, 80:20 CH_2Cl_2/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2956, 1672, 1454, 1365, 1201, 1079, 1048; ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm) 3.77 (s, 3H) 3.71−3.77 (m, 1H), 2.26−2.48 (m, 2-H), 2.02−2.20 (m, 2H), 1.53−1.85 (m, 5H), 1.32−1.41 (m, 1H), 0.86 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 167.3, 63.1, 61.8, 55.0, 39.2, 32.7, 32.4, 31.6, 27.3, 26.7, 25.5; HRMS (EI) calcd $C_{13}H_{23}NO_2$ for [M^+] 225.1729, found 225.1717.

***tert*-Butyl 3-(2-(Methoxyamino)cyclopentyl)propanoate (25a,b).** Prepared according to the general procedure described above from

oxime **8** (100 mg, 0.79 mmol, 1 equiv), *tert*-butyl iodoacetate **24** (573 mg, 2.37 mmol, 3 equiv), and triethylborane (1.0 M in hexane, 2.37 mL, 2.37 mmol, 3 equiv) in CH_2Cl_2 (7.9 mL) at −20 °C. Flash chromatography (silica gel, 92:8 → 50:50 petroleum ether/AcOEt) afforded major diastereomer **25a** (26 mg, 14%), a mixture of **25a** and **25b** (85 mg, 44%), and minor diastereomer **25b** (6 mg, 3%) (total combined yield, 117 mg, 61%) all as yellow oils. Integration on the ^{13}C NMR crude spectra showed a 66:34 mixture of **25a/25b**. Major diastereomer **25a**: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.42 (bs, 1H), 3.49 (s, 3H), 3.38 (q, J = 5.5 Hz, 1H), 2.25 (dt, J = 2.0, 8.7 Hz, 2H), 1.65−1.84 (m, 5H), 1.29−1.63 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.4, 80.1, 62.9, 61.9, 42.9, 34.8, 29.9, 29.6, 28.2 (3C), 24.5, 22.0. Minor diastereomer **25b**: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.79 (bs, 1H), 3.72 (s, 3H), 3.20−3.26 (m, 1H), 2.28 (t, J = 7.2 Hz, 2H), 1.40−1.95 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.7, 80.7, 67.3, 62.5, 42.3, 34.4, 31.7, 30.0, 28.8, 28.3, 23.8; IR (neat) ν_{max} (cm^{-1}) 2937, 2871, 1729, 1455, 1367, 1256, 1155, 848; HRMS (TOF MS) calcd for $C_{13}H_{25}NO_3Na$ [M + Na^+] 266.1726, found 266.1728.

3-[2-(Dimethylphenylsilanyl)-5-methoxyaminocyclopentyl]propionic Acid *tert*-Butyl Ester (26). Prepared according to the general procedure described above from allylsilane oxime **8** (0.100 g, 0.38 mmol, 1 equiv), *tert*-butyl iodoacetate **24** (0.18 mg, 0.76 mmol, 2 equiv), and triethylborane (1.0 M in hexane, 0.76 mL, 0.76 mmol, 2 equiv) in CH_2Cl_2 (3.8 mL) at −20 °C. Flash chromatography (silica gel, 92:8 → 50:50 petroleum ether/AcOEt) afforded the title compound **26** as a yellow oil (0.144 g, 74%): R_f = 0.25 (silica gel, 90:10 petroleum ether/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2937, 1727, 1366, 1250, 1149, 830; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47−7.52 (m, 2H), 7.31−7.35 (m, 3H), 5.85 (bs, 1H), 3.49 (s, 3H), 3.34 (q, J = 4.9 Hz, 1H), 2.09−2.30 (m, 2H), 1.73−1.96 (m, 2H), 1.40−1.70 (m, 14H), 1.09−1.70 (m, 1H), 0.29 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.2, 138.5, 133.8, 128.8, 127.6, 79.9, 67.8, 62.9, 62.0, 44.0, 34.3, 29.9, 28.0, 25.2, 24.9, −4.1, −4.4; HRMS (LSIMS) calcd for $C_{21}H_{36}NO_3Si$ [M + H^+] 378.2464, found 378.2460.

3-[3-Acetoxy-2-(dimethylphenylsilanyl)-5-methoxyaminocyclopentyl]propionic Acid *tert*-Butyl Ester (27). Prepared according to the general procedure described above from allylsilane oxime **6** (0.30 mg, 0.94 mmol, 1 equiv), *tert*-butyl iodoacetate **24** (0.455 g, 1.88 mmol, 2 equiv), and triethylborane (1.0 M in hexane, 2.7 mL, 2.7 mmol, 6 equiv) in CH_2Cl_2 (10 mL). Flash chromatography (silica gel, 85:15 → 30:60 petroleum ether/EtOAc) afforded the title compound **27** as a yellow oil (0.21 g, 51%) and recovered starting material (0.112 g, 37%): R_f = 0.44 (silica gel, 60:40 petroleum ether/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2976, 1732, 1369, 1250, 1151, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.49−7.51 (m, 2H), 7.26−7.33 (m, 3H), 5.47 (bs, 1H), 5.31 (dt, J = 3.0, 6.8 Hz, 1H), 3.55 (q, J = 6.4 Hz, 1H), 3.49 (s, 3H), 2.07−2.25 (m, 4H), 1.85 (s, 3H), 1.74 (dd of ABq, J = 2.6, 6.4, 14.7 Hz, 1H), 1.48−1.64 (m, 3H), 1.42 (s, 9H), 0.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.9, 170.2, 139.0, 133.5, 128.9, 127.7, 80.1, 78.2, 61.8, 61.1, 43.5, 39.0, 35.4, 34.1, 28.1, 24.6, 21.1, −2.3, −2.9; HRMS (TOF ESI) calcd for $C_{23}H_{37}NO_5SiNa$ [M + Na^+] 458.2339, found 458.2341.

5-(Dimethylphenylsilanyl)-3,3-difluoro-1-methoxyoctahydro-[1]pyridin-2-one (29). Prepared according to the general procedure described above from allylsilane oxime **4** (0.100 g, 0.38 mmol, 1 equiv), ethyl bromodifluoroacetate **28** (0.154 g, 1.88 mmol, 2 equiv), and triethylborane (1.0 m in hexane, 2.4 mL, 2.4 mmol, 5 equiv) in CH_2Cl_2 (10 mL). Flash chromatography (silica gel, 99:1 → 98:2 CH_2Cl_2/EtOAc) afforded lactam **29** as a yellow oil (0.069 g, 53%) and recovered oxime **4** (0.019 g, 71% yield based on recovered starting material): R_f = 0.17 (silica gel, 98:2 CH_2Cl_2/EtOAc); IR (neat) ν_{max} (cm^{-1}) 3398, 1704, 1428, 1250, 1114, 1001; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.48−7.51 (m, 2H), 7.36−7.41 (m, 3H), 3.75−3.83 (m, 4H), 2.37−2.48 (m, 1H), 1.68−2.22 (m, 5H), 1.40−1.54 (m, 1H), 1.17−1.26 (m, 1H), 0.33 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.4 (t, J = 30.7 Hz, 1C), 136.6, 133.6, 129.5, 128.0, 112.3 (t, J = 244.2, 249.2 Hz, 1C), 63.5, 61.8, 35.7, (t, J = 22.0 Hz, 1C) 34.0 (dd, J = 2.7, 6.0 Hz, 1C), 32.1, 30.5, 25.9, −4.7, −5.1; HRMS (TOF ESI) calcd for $C_{17}H_{24}F_2NO_2Si$ [M + H^+] 340.1544, found 340.1553.

Acetic Acid 5-(Dimethylphenylsilanyl)-3,3-difluoro-1-methoxy-2-oxooctahydro[1]pyridin-6-yl Ester (30). Prepared according to the general procedure described above from allylsilane oxime **6** (0.30 g, 0.94 mmol, 1 equiv), ethyl bromodifluoroacetate **28** (0.24 mL, 1.88 mmol, 2 equiv), and triethylborane (1.0 M in hexane, 2.4 mL, 2.4 mmol, 5 equiv) in CH_2Cl_2 (10 mL). Flash chromatography (silica gel, 75:25 → 25:75 petroleum ether/EtOAc) afforded title compound **30** as a yellow oil (0.24 g, 65%): IR (neat) ν_{max} (cm^{-1}) 3356, 2958, 1669, 1432, 1253, 1094; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47−7.50 (m, 2H), 7.37−7.39 (m, 3H), 5.40 (t, J = 5.3 Hz, 1H), 4.22 (q, J = 6.8 Hz, 1H), 3.8 (s, 3H), 2.75 (quint, J = 7.9 Hz, 1H), 2.40 (d of ABq, J = 6.4, 13.9 Hz, 1H), 1.91 − 2.09 (m, 6H), 1.56 (t, J = 6.8 Hz, 1H), 0.42 (s, 3H), 0.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 169.8, 158.5 (t, J = 31.3 Hz, 1C), 136.7, 133.4, 129.7, 128.2, 112.1 (t, J = 244.4 Hz, 1C), 62.0, 61.4, 39.5, 37.4, 35.3, (t, J = 22.0 Hz, 1C), 33.5, 21.1, − 3.4, − 3.5; HRMS (EI) calcd. for $C_{18}H_{22}NO_4F_2Si$ [M^+ − CH_3] 382.1286, found 382.1274; HRMS (EI) calcd for $C_{13}H_{20}NO_4F_2Si$ [M^+ − C_6H_5] 320.1130, found 320.1145.

5-Hydroxy-1-methoxyoctahydro[1]pyridin-2-one (31). To a solution of silyl lactam **16a** (1.66 g, 5.46 mmol, 1 equiv) in AcOH (29 mL) at 5 °C were added sodium acetate (1.34 g, 16.4 mmol, 3 equiv) and potassium bromide (1.17 mg, 9.8 mmol, 1.8 equiv). Peracetic acid (5.0 mL, 27 mmol, 5 equiv) was then added to the viscous solution. The resulting orange solution was then allowed to warm to room temperature. Sodium acetate (4.5 g, 55 mmol, 10 equiv) and peracetic acid (18 mL, 98 mmol, 18 equiv) were then again added, and the resulting mixture was stirred at room temperature overnight (ca. 15 h). The orange color disappeared after a few hours, and saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ (1:1) was carefully added. The resulting mixture was concentrated in vacuo. Purification by flash chromatography (silica gel, 98:2→80:20 CH_2Cl_2/MeOH) afforded the desired alcohol **31** (0.83 g, 82% yield) as a yellow oil: R_f = 0.38 (90:10 CH_2Cl_2/MeOH); ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 4.23 (q, J = 7.0 Hz, 1H), 4.11 (q, J = 3.9 Hz, 1H), 3.74 (s, 3H), 2.01−2.44 (m, 6H), 1.55−1.91 (m, 4H); ^{13}C NMR (250 MHz, $CDCl_3$) δ (ppm) 167.2, 76.3, 61.5, 60.8, 47.4, 37.7, 31.4, 29.4, 21.7; HRMS (EI) calcd for $C_9H_{15}NO_3$ [M^+] 185.10519, found 185.1052.

3-[5-(Dimethylphenylsilanyl)-2-(ethoxycarbonylmethyl-methoxyamino)-2-ethylcyclopentyl]propionic Acid Ethyl Ester (33). Prepared according to the general procedure described above from allylsilane oxime **32** (580 mg, 2.0 mmol, 1 equiv), ethyl iodoacetate **13** (0.52 mL, 4.4 mmol, 2.2 equiv), and triethylborane (1.0 M in hexane, 5.0 mL, 5.0 mmol, 2.5 equiv) in CH_2Cl_2 (1.5 mL). Flash chromatography (silica gel, 10:1 → 7:1 petroleum ether/EtOAc) afforded the title compound **33** as a yellow oil (0.927 g, 82%): R_f = 0.35 (silica gel, 10:1 petroleum ether/EtOAc): IR (neat) ν_{max} (cm^{-1}) 2953, 1732, 1464, 1428, 1373, 1188, 1037; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.48 − 7.51 (m, 2H), 7.32−7.34 (m, 3H), 4.18 (q, J = 7.2 Hz, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.55 (m, 5H), 2.22−2.45 (m, 2H), 1.11−1.91 (m, 15H), 0.78−0.90 (m, 4H), 0.30 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.9, 171.1, 138.5, 133.9, 128.9, 127.7, 75.6, 62.1, 60.6, 60.0, 58.9, 47.6, 32.4, 32.1, 31.8, 28.3, 27.5, 26.2, 14.2, 14.1, 9.3, −3.8; HRMS (TOF ESI) calcd for $C_{25}H_{41}NO_5SiNa$ [M + Na^+] 428.2652, found 428.2656.

5-[3-(Dimethylphenylsilanyl)-2-(2-ethoxycarbonylethyl)-1-(ethoxycarbonylmethylmethoxyamino)cyclopentyl]pent-2-enoic Acid Ethyl Ester (40). To a solution of oxime **37** (50 mg, 0.13 mmol, 1 equiv) in CH_2Cl_2 (2 mL) (not degassed) under an N_2 atmosphere was added ethyl iodoacetate **13** (0.046 mL, 0.38 mmol, 3 equiv), and Et_3B (1 M in hexane) was added by portions every 15 min (14 × 0.4 equiv, total of 5.6 equiv, 0.7 mL, 0.7 mmol). The resulting mixture was then diluted with CH_2Cl_2 and quenched with saturated

aqueous $NaHCO_3$. Layers were separated, and the organic phase was washed with saturated aqueous NaCl (1×), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (silica gel, 91:9 → 83:17 petroleum ether/AcOEt) afforded the title compound **40** as a yellow oil (42 mg, 68%): R_f = 0.15 (91:9 petroleum ether/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.45−7.48 (m, 2H), 7.31−7.35 (m, 3H), 6.62 (ddd, J = 6.8, 8.7, 15.5 Hz, 1H), 5.61 (d, J = 15.8 Hz, 1H), 4.06−4.23 (m, 6H), 3.54 (s, 3H), 3.51 (s, 2H), 1.15−2.47 (m, 22H), 0.72−0.92 (m, 1H), 0.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.8, 170.7, 166.7, 149.3, 137.7, 134.0, 129.3, 127.8, 120.8, 74.9, 62.7, 60.6, 60.1, 60.0, 56.6, 48.5, 33.1, 32.6, 32.0, 31.2, 28.1, 27.5, 25.6, 14.3, 14.2, 14.1, − 3.5, − 3.8; HRMS (TOF ESI) calcd for $C_{30}H_{47}NO_7SiNa$ [M + Na^+] 584.3020, found 584.3021.

6-[3-(Dimethylphenylsilanyl)-2-(2-ethoxycarbonylethyl)-1-(ethoxycarbonylmethylmethoxyamino)cyclopentyl]-hex-2-enoic Acid Ethyl Ester (41). To a solution of oxime **38** (70 mg, 0.174 mmol, 1 equiv) in CH_2Cl_2 (2 mL) (not degassed) under an N_2 atmosphere was added ethyl iodoacetate **13** (0.054 mL, 0.45 mmol, 4 equiv), and Et_3B (1 M in hexane) was added by portions every 15 min (10 × 0.5 equiv, total of 5 equiv, 0.9 mL, 0.9 mmol). The resulting mixture was then diluted with CH_2Cl_2 and quenched with saturated aqueous $NaHCO_3$. Layers were separated, and the organic phase was washed with saturated aqueous NaCl (1×), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (silica gel, 91:9 petroleum ether/AcOEt) afforded the title compound **41** as a yellow oil (61 mg, 72%): R_f = 0.16 (91:9 petroleum ether/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47−7.49 (m, 2H), 7.32−7.35 (m, 3H), 6.85 (ddd, J = 6.8, 8.7, 15.5 Hz, 1H), 5.73 (d, J = 15.5 Hz, 1H), 4.05−4.22 (m, 6H), 3.53 (s, 3H), 3.50 (s, 2H), 2.35−2.46 (m, 1H), 2.13−2.23 (m, 1H), 1.57−1.91 (m, 5H), 1.1−1.6 (m, 17H), 0.85−0.95 (m, 1H), 0.29 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.9, 170.8, 166.6, 149.1, 138.1, 134.1, 129.1, 127.8, 121.3, 75.0, 62.5, 60.6, 60.0, 56.7, 48.4, 34.9, 32.9, 32.6, 32.0, 31.2, 28.1, 25.7, 23.2, 14.3, 14.2, 14.1, − 3.5, − 3.7; HRMS (TOF ESI) calcd for $C_{31}H_{49}NO_7SiNa$ [M + Na^+] 598.3176, found 598.3179.

3-[2-(Benzylmethoxyamino)-5-(dimethylphenylsilanyl)-2-ethylcyclopentyl]propionic Acid Ethyl Ester (43). To a solution of oxime **32** (100 mg, 0.35 mmol, 1 equiv) in CH_2Cl_2 (3.5 mL) was added Et_3B (1 M in hexane, 3.5 mL, 2.5 mmol, 10 equiv). The septum was then removed and the flask opened to the air. A solution of ethyl iodoacetate was added and the mixture stirred for 2 h at room temperature. TLC analysis indicated incomplete consumption of the starting material, and additional ethyl iodoacetate **13** (113 mg, 0.52 mmol, 1.5 equiv) and benzyl iodide **42** (381 mg, 1.75 mmol, 5 equiv) were then added slowly via syringe pump over 40 min. This operation was repeated a third time 2 h later. The mixture was then concentrated in vacuo. Purification by flash chromatography (silica gel, gradient 99:1→80:20 petroleum ether/EtOAc) yielded recovered starting material (46 mg) and a 1:3 mixture of silyl cyclopentane **43** and side product $PhCH_2CH_2Ph$ (bibenzyl) as a colorless oil. Upon heating of the latter mixture at 70 °C under vacuum (0.2 mbar) overnight, a pure **43** (46 mg, 28% yield, 58% yield based on recovered starting material) was obtained as a yellow oil: R_f = 0.36 (88:12 petroleum ether/EtOAc): IR (neat, NaCl) ν_{max} (cm^{-1}) 2957, 1732, 1454, 1428, 1250, 1180, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.41−7.60 (m, 4H), 7.19−7.40 (m, 6H), 4.12 (q, J = 7.2 Hz, 2H), 3.90 (s, 2H), 3.10 (s, 3H), 2.24−2.47 (m, 2H), 1.99−2.18 (m, 2H), 1.53−1.86 (m, 5H), 1.19−1.50 (m, 6H), 0.87 (t, J = 7.5 Hz, 3H), 0.34 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.1, 140.0, 138.9, 134.0, 129.5, 129.0, 128.1, 127.8, 126.9, 75.8, 62.9, 60.2, 58.5, 48.0, 37.3, 32.2, 32.1, 28.7, 27.8, 26.5, 14.4, 9.6, −3.5, −3.7; HRMS (TOF) calcd for $C_{28}H_{41}NO_3NaSi$ [M + Na^+] 490.2753, found 490.2753.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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