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Cyclic Enecarbamates as Precursors of α,β-Unsaturated Iminium Ions: Reactivity and Synthesis of 6,6-Spirocyclic Ring Systems

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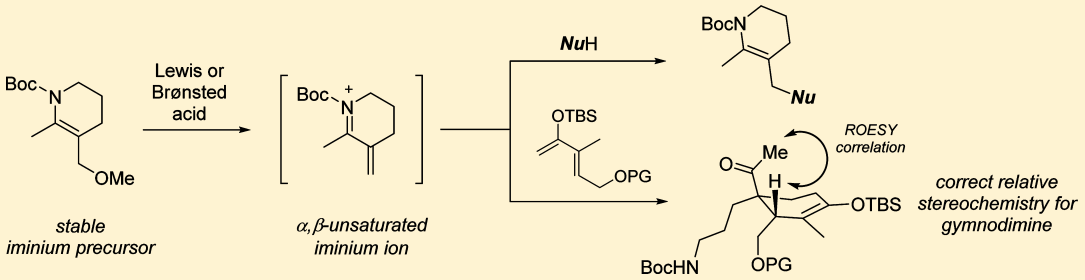
Supporting Information



ABSTRACT: The scalable synthesis of cyclic enecarbamates and their use as convenient precursors of α,β-unsaturated *N*-acyl iminium ions is reported. The newly developed route overcomes synthetic and reactivity difficulties in previously reported methods, is readily scaled up, and proceeds through stable intermediates suitable for long-term storage if required. Preliminary investigations probing the reactivity of cyclic α,β-unsaturated *N*-acyl iminium ions as dienophiles in Diels–Alder reactions and electrophilic alkylating agents are described. In the presence of Lewis and Brønsted acids, iminium precursor **22a** underwent efficient Diels–Alder cycloaddition with a range of simple and complex dienes, culminating in the synthesis of 6,6-spirocyclic ring systems possessing the same relative stereochemistry as the spirocyclic imine present in the marine natural product gymnodimine **1**.

INTRODUCTION

N-Acyl iminium ions are well established as versatile and effective reactive intermediates in the synthesis of nitrogen-containing compounds and have been widely used in natural product synthesis and medicinal chemistry.[1] α,β-Unsaturated *N*-acyl iminium ions form a less well-known subset of the wider compound class.[2] The intramolecular cycloadditions of α,β-unsaturated iminium ions have previously been applied in total synthesis of natural products, including gymnodimine **1**[3] and symbioimine **2**[4] (Figure 1), but the intermolecular variant is to date much less developed. A seminal study of α,β-unsaturated *N*-H iminium salts as intermolecular Diels–Alder dienophiles has been reported by Evans in work directed toward the marine natural product spiro prorocentrimine **3**.[5] Given the vast literature surrounding *N*-acyl iminium ion chemistry, greater understanding of α,β-unsaturated *N*-acyl iminium species and effective methods for their preparation and use would potentially be of great synthetic utility.

In principle α,β-unsaturated *N*-acyl iminium ions may be formed by elimination of a nucleofuge from either the α or γ position (Scheme 1). In particular, our group has previously investigated *N*-acyl iminium chemistry in the context of both natural product synthesis and novel method development. Our earlier studies involved the use of *N*-acyl *N*,*O*-acetals as precursors of reactive dienophiles for Diels–Alder reactions,[6] and the synthesis and reactivity of β-methoxymethyl *N*-acyl enecarbamates.[7]

Although the Diels–Alder cycloaddition of **8** and **9** to give **10** was a notable milestone in the development of an α,β-unsaturated *N*-acyl iminium approach to the 6,6-spirocyclic imime ring system of gymnodimine **1**, a number of important problems remained to be addressed. The preparation of iminium precursors **5** and **7** was inefficient and proceeded through unstable intermediates. In addition, the crucial relative stereochemistry between the quaternary center and the protected hydroxyl methyl substituent was opposite to that required for the natural product. As a result it appeared that development of a new scalable method for access to α,β-unsaturated *N*-acyl iminium ion precursors would be necessary to enable further studies toward the synthesis of spirocyclic imines and provide access to structures possessing the correct stereochemistry required for **1**.

The introduction of a methyl group at the imine center appeared likely to increase the hydrolytic stability of any iminium ion precursors and intermediates involved in their

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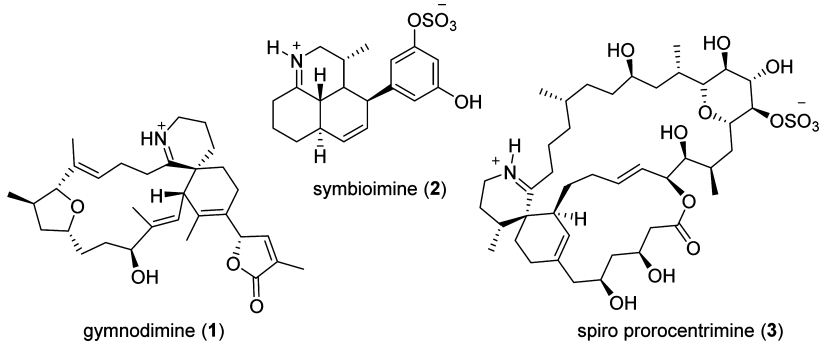
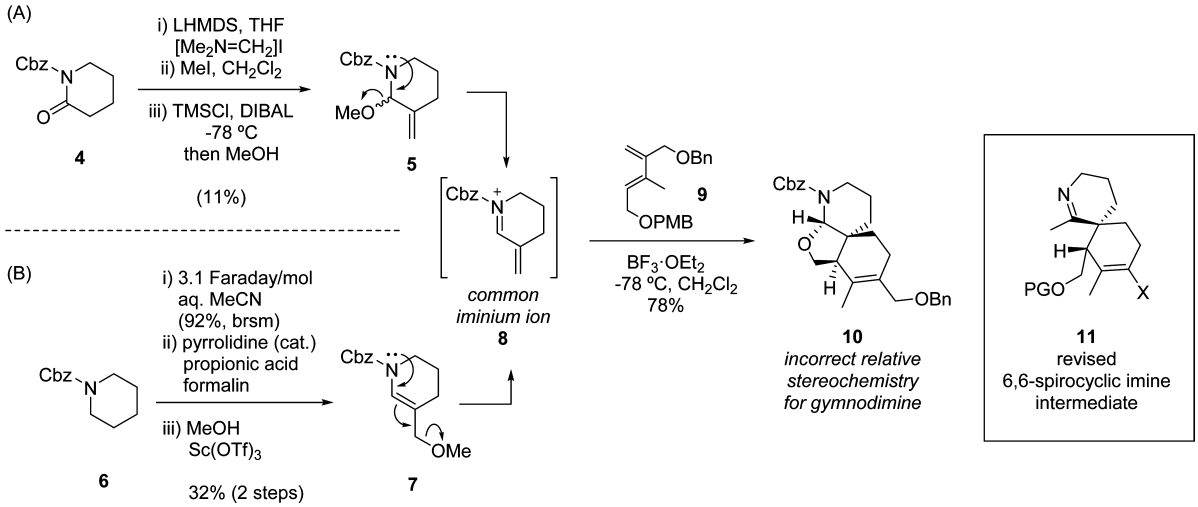


Figure 1. Natural products potentially accessed via α,β-unsaturated iminium chemistry.

Scheme 1. α,β-Unsaturated *N*-Acyl Iminium Ion Chemistry Towards the 6,6-Spirocyclic Imine Fragment of Gymnodimine 1 Reported Previously by Our Group,[6,7] and Revised Intermediate 11



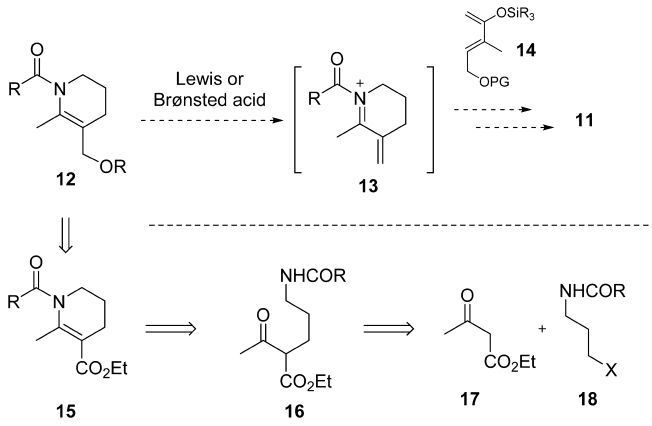
preparation. This methyl group might also provide a useful synthetic handle for subsequent elaboration toward the complete natural product framework.[8] Further, it was envisaged that the iminium carbon might be rendered less susceptible to nucleophilic attack of the protected alcohol in diene **9**, an interaction that potentially contributed to the undesired stereochemical outcome of cycloaddition in **10**. Diene **9** itself required a relatively lengthy synthesis that limited access to multigram quantities for synthesis. Revising the structure of the diene partner to 2-silyloxy butadiene **14** (Scheme 2) was expected to enable a more process-friendly synthesis, suitable for supporting ongoing synthetic studies. It was further expected that diene **14** would exhibit greater reactivity in comparison to **9** in the cycloaddition step.

In applying these design criteria, we expected that an iminium ion such as **13** could be generated from hydroxymethyl enecarbamate derivative **12** on exposure to a Lewis or Brønsted acid (Scheme 2). Further, the *N*-acyl vinylogous amide motif was expected to confer increased stability to ester **15**, rendering it suitable for scale-up and storage. Iminium precursor **12** would be available from partial reduction of **15**, which in turn was likely to be accessible on scale via substituted β-ketoester **16**, from readily available starting materials **17** and **18**.

RESULTS AND DISCUSSION

Synthesis commenced with alkylation of ethyl acetoacetate (Scheme 3) using known *N*-Boc iodide **19**. Use of the

Scheme 2. Generation of the α,β-Unsaturated Iminium Ion 13 from Proposed General Precursor 12, and Retrosynthetic Analysis of Proposed Intermediate Enecarbamate Ester 15



corresponding iodoazide was also considered, but not pursued.[9] Initial experiments revealed that the Boc-protected nitrogen of **20** was not nucleophilic enough to effect cyclization to enecarbamate **21**, but this transformation was achieved readily by TFA deprotection and careful neutralization with aqueous bicarbonate. Subsequent *N*-Boc protection of **21** required fairly forcing conditions to complete the synthesis of ester **22** in 83% yield over three steps from β-ketoester **20**.

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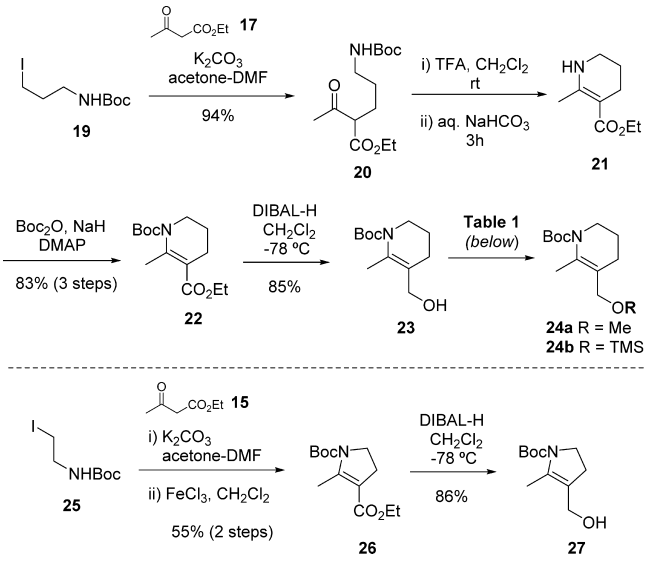
Scheme 3. Synthesis of Stable Six- and Five-Membered Enecarbamates 22 and 26 and Corresponding Iminium Ion Precursor Candidates 23, 24a,b, and 27



Although the Boc removal−reprotection sequence initially appeared inefficient, the high overall yield for the sequence and ease of access to these materials on scale allowed convenient preparation of >20 g amounts of **22** for ongoing study. In addition, access to unprotected vinylogous amide **21** would be necessary in later investigations into the role of the *N*-acyl group on iminium formation and reactivity. The corresponding five-membered iminium precursor **27** was also prepared, beginning from *N*-Boc iodide **25** (Scheme 3). In this case, however, during purification some spontaneous cyclization of the initial ethyl acetoacetate alkylation product to **26** was observed. This two-step, one-pot sequence was readily optimized to directly afford **26** in high yield. Reduction of the ester to afford alcohol **27** proceeded in a straightforward manner, as found for the six-membered case.

In order to probe the influence of the leaving group on iminium ion generation, a brief survey of derivatives of alcohol **23** was investigated (Table 1). Electron-donating substituents were able to be introduced in excellent yield, to afford the methyl ether **24a** (Table 1, entry 1) and trimethylsilyl ether **24b** (Table 1, entry 2). Derivatives of **23** with more electron-withdrawing groups such as acetate (Table 1, entry 3) and benzoate (Table 1, entry 4) were not stable to isolation. In the case of the proposed tosylate derivative (Table 1, entry 5), attempted purification resulted in clean conversion to enone **31** via hydrolysis of the intermediate iminium.

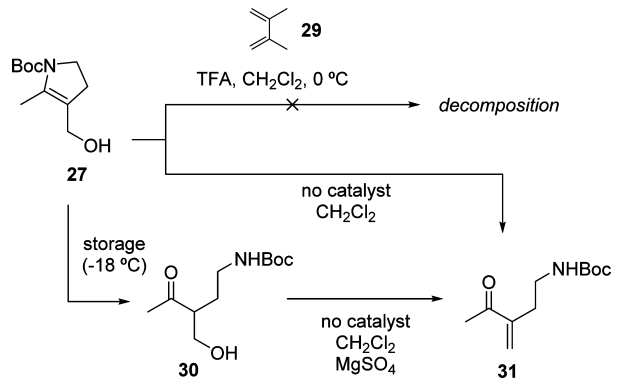
Table 1. Effect of Hydroxy Group Modification of 23 (Scheme 3)

entry	R	conditions	product (%)
1	Me	MeI, NaH, THF, 45 °C	**24a** (81)
2	TMS	TMSCl, NEt_3, CH_2Cl_2	**24b** (79)
3	Bz	BzCl, NEt_3, DMAP, CH_2Cl_2	-[a]
4	Ac	Ac_2O, NEt_3, DMAP, CH_2Cl_2	-[a]
5	Ts	TsCl, NEt_3, DMAP, CH_2Cl_2	 **28**

[a] ^{1}H NMR of crude product exhibited resonances for expected product, but decomposed on further manipulation.

With reliable access to iminium precursors **23** and **24a** established, an initial study was undertaken to determine conditions for generation and reaction of the corresponding α,β-unsaturated acyl iminium ions (Scheme 4). Disappointingly, exposure of five-membered iminium precursor **27** to trifluoroacetic acid in the presence of excess 2,3-butadiene **29** resulted in extensive decomposition. In control reactions without any acid present, **27** was found to convert cleanly to enone **31**, even in the presence of drying agents. Further, **27** was observed to convert to β-hydroxy ketone **30** via hydration and ring opening on overnight storage at −18 °C under a nitrogen atmosphere. Isolated **30** was found to be readily transformed to enone **31** under very mild conditions in the presence of a drying agent.

Scheme 4. Hydrolysis Products Generated from Five-Membered Iminium Precursor 27 upon Attempted Cycloaddition or Storage



These studies indicated that five-membered iminium precursor **27** was relatively unstable under even mild conditions. Rapid decomposition in the presence of acid suggested that unproductive intramolecular reaction pathways had prevented the desired cycloaddition taking place, although no information about the nature of these was able to be obtained. Given these problems, and our ongoing interest in 6,6-spirocyclic imines related to gymnodimine **1**, we next focused our efforts on the six-membered congeners **23** and **24a** that would potentially give access to the target ring structure via a Diels−Alder cycloaddition.

We were pleased to find that treatment of iminium precursor **23** with trifluoroacetic acid in the presence of excess 2,3-butadiene (Scheme 5) afforded predominantly Diels−Alder product **34** (Table 2, entry 1) that had undergone hydrolytic ring opening of the presumed postcycloaddition iminium intermediate **33**. Although the use of boron trifluoride, TMSOTf, and anhydrous HCl only resulted in decomposition (Table 2, entries 2, 3, and 9), both the Brønsted acid PTSA (Table 2, entry 4) and the Lewis acids indium trichloride (Table 2, entry 6), zirconium chloride (Table 2, entry 7), and iron trichloride (Table 2, entry 8) also successfully promoted the Diels−Alder reaction, in all cases accompanied by hydrolytic ring opening. In contrast to other reagents, use of the weak Brønsted acid PPTS cleanly gave enone **28**, the direct hydrolysis product of iminum ion **30**. A solvent screen using the successful trifluoroacetic acid conditions (Table 2, entry 1) revealed that the Diels−Alder reaction only proceeded to give

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Scheme 5. Diels–Alder Cycloaddition of Six-Membered α,β-Unsaturated Iminium Ion 32

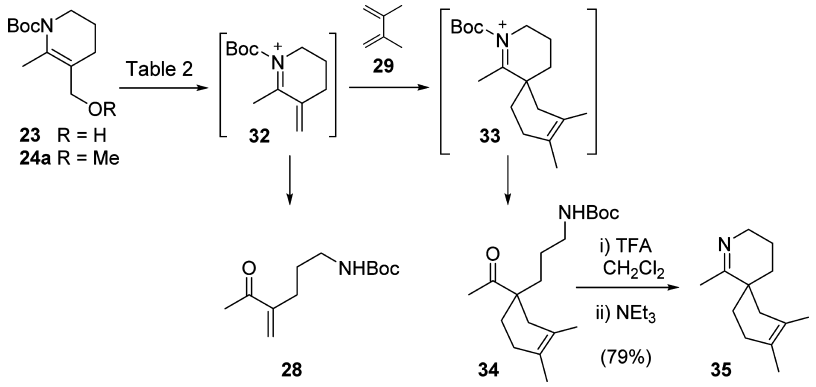


Table 2. Preliminary Qualitative Screen of Iminium Diels–Alder Conditions

entry	sm	conditions[a]	28:34:dec[b,c]
1	23	TFA	34[d]
2		$BF_3{\cdot}OEt_2$	dec
3		TMSOTf	dec
4		PTSA	34[d]
5		PPTS	28
6		$InCl_3$	34[d]
7		$ZrCl_4$	34[d]
8		$FeCl_3$	34[d]
9		3 M HCl[e]	dec
10	24a	TFA	28
11		$ZrCl_4$	dec
12		$BF_3{\cdot}OEt_2$	34[d]
13		$Sc(OTf)_3$	34[c,f]

[a]Test reactions were carried out in CH_2Cl_2 (except for entry 13) at rt for 18 h with acid promoter (*ca.* 1 equiv) and 2,3-butadiene **29** (5 equiv). [b]Decomposition. [c]Qualitative parallel study; yields not determined. [d]Some decomposition also observed. [e]Anhydrous solution in EtOAc. [f]Reaction run in MeCN.

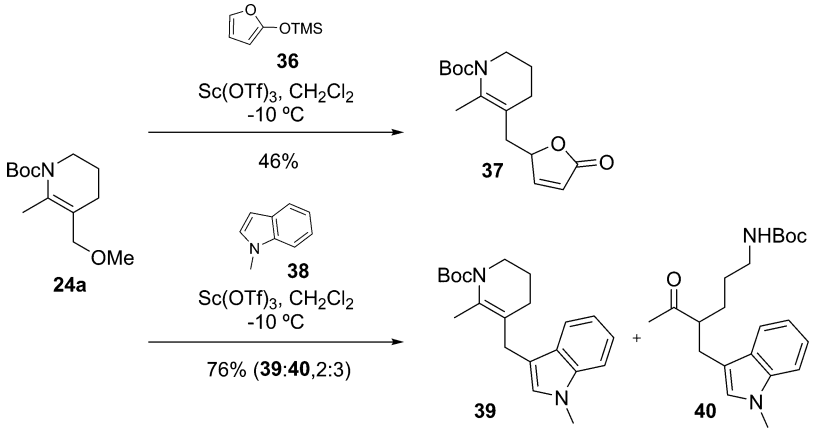
34 in dichloromethane or acetonitrile. All other solvents investigated (DMF, DMSO, dioxane, toluene, THF, and diethyl ether) cleanly gave the ring-opened enone **28**. Ring-opened Diels–Alder product **34** was able to be converted to 6,6-spirocyclic imine **35** in 79% yield, by *N*-Boc deprotection and subsequent treatment with triethylamine.

Use of the β-methoxy iminium precursor **24a** was also found to successfully deliver Diels–Alder product **34**, although interestingly the best conditions identified for reaction of **23** in this case resulted only in the formation of enone **28** (Table 2, entry 10). Reaction with zirconium chloride (Table 2, entry 11) afforded an inseparable mixture of many products. Finally, both boron trifluoride (Table 2, entry 12) and scandium triflate in acetonitrile (Table 2, entry 13) gave clean formation of the desired cycloaddition product, **34**.

Further confirmation of the synthetic utility of **24a** was obtained through Lewis acid mediated generation of the iminium ion in the presence of nucleophiles (Scheme 6). Reaction with 2-trimethylsilyloxyfuran **36** gave the expected enecarbamate adduct **37**, while reaction with *N*-methylindole **38** afforded both enecarbamate **39** and its hydrolysis product methyl ketone **40**, in good combined yield.

Following these investigations, we were confident that the *N*-Boc iminium chemistry would prove useful in ongoing synthetic studies. Our observations indicated that both six-membered **23** and **24a** could be used as iminium precursors. For further study of the Diels–Alder cycloaddition as a means to access the 6,6-spirocyclic imine ring system we chose to use methyl ether analogue **24a**, as it exhibited a slightly better reactivity profile and stability to storage. The synthesis proved to be scalable and robust, allowing multigram amounts of enecarbamate ester **22** to be synthesized and stored. Iminium

Scheme 6. Reaction of Iminium Precursor 24a with Nucleophiles[a]



[a]Yields are unoptimized.

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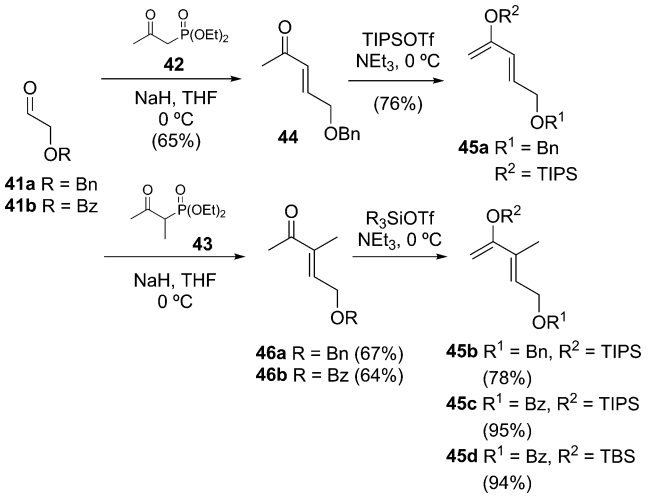
precursor **24a** was synthesized on gram scale as required and could be stored for 2−3 weeks, refrigerated under nitrogen.

In order to investigate the synthesis of 6,6-spirocyclic imine systems via a *N*-acyl iminium Diels−Alder reaction of **24a**, a series of 2-silyloxy dienes were prepared (Scheme 7). Horner−

Scheme 7. Synthesis of 2-Silyloxy Dienes 45a−d



Wadsworth−Emmons condensation of aldehyde **41a** or **41b** with phosphonate **42** or **43** afforded the expected α,β-unsaturated methyl ketones **44**, **46a**, and **46b**. These were then readily transformed to the corresponding enol ether dienes **45a−d** on treatment with the appropriate silyl triflate and triethylamine.

Attempts at Diels−Alder cycloaddition of **24a** with diene **45a** (Scheme 8) were initially unpromising. Reaction in the presence of scandium triflate gave only the iminium ion hydrolysis product, enone **28**, along with ketone **44** resulting from desilylation of the enol ether (Table 3, entry 1). The use of boron trifluoride also appeared equally unsatisfactory (Table 3, entry 2); however, after careful chromatographic purification of the crude product mixture, we were pleased to isolate a trace amount of enecarbamate cycloaddition product **48a**, exhibiting a molecular ion at m/z 555.86. In the proton NMR spectrum, the exocyclic methylene protons gave two distinctive signals at δ 3.35 and δ 3.87 ppm, and the methylene protons α to the nitrogen (H_a, H_b) resonated at markedly different chemical shifts (δ 2.90 and 4.11 ppm), indicative of a cyclic system.

Table 3. Successful Diels−Alder Cycloaddition of 24a and Dienes 45a−d

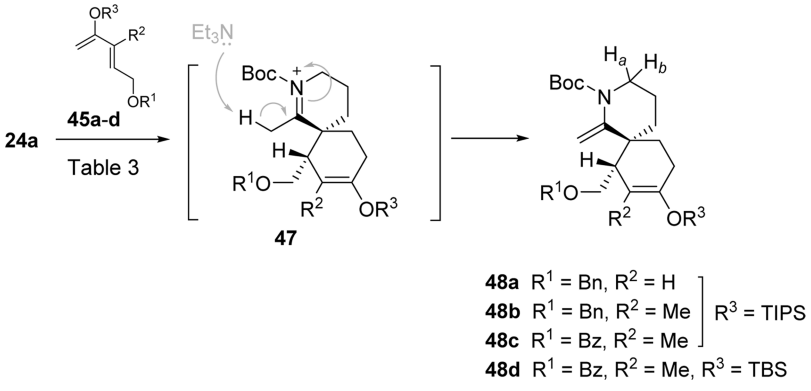
entry	diene	conditions[a]	yield (%)
1	**45a**	$Sc(OTf)_3$, MeCN	**28**[b]
2	**45a**	$BF_3{\cdot}OEt_2$, CH_2Cl_2	**48a** (<5)[b]
3	**45b**	$ZnCl_2$, CH_2Cl_2 + Et_3N[c]	**48b** (20)[b]
4	**45b**	$BF_3{\cdot}OEt_2$, CH_2Cl_2 + Et_3N[c]	**48b** (34)[b]
5	**45c**	$BF_3{\cdot}OEt_2$, CH_2Cl_2 + Et_3N[c]	**48c** (76)[b]
6	**45d**	$BF_3{\cdot}OEt_2$, CH_2Cl_2 + Et_3N[c]	**48d** (75)[b]

[a]Reactions run at −78 °C except for entry 1 at −35 °C. [b]The ketone derivative of the relevant starting 2-silyloxy diene **44**, **46a**, or **46b** was observed in every reaction. [c]NEt_3 (10 equiv) added after 60 min, at −78 °C.

As enecarbamate **48a** most likely arose from deprotonation of the spirocyclic iminium species **47**, resulting from cycloaddition of the initial iminium ion **32** with diene **45a**, it seemed reasonable that addition of an organic base to the reaction mixture should favor the formation of **48a**. Having confirmed that **48a** was stable to chromatography, we anticipated that this would enable higher-yielding isolation of the cycloaddition products. Accordingly, the reaction of iminium precursor **24a** with diene **45b**, possessing the 3-methyl substituent required for gymnodimine, was quenched after 1 h at −78 °C with 10 equiv of triethylamine. Pleasingly, enecarbamate **48b** was isolated in a slightly increased yield of 20% (Table 3, entry 3), which was further improved to 34% with the use of boron trifluoride as the Lewis acid (Table 3, entry 4). Reasoning that the nucleophilicity of the benzyl protected alcohol in dienes **45a** and **45b** could be exerting a deleterious influence on the reaction with the highly electrophilic iminium species, the reaction was repeated using diene **45c** possessing a benzoyl protecting group (Table 3, entry 5). We were pleased to find in this case enecarbamate **48c** was isolated in 76% yield, as a single diastereoisomer. The reaction proceeded similarly with TBS protected diene **45d**, to afford enecarbamate **48d**, again as a single diastereoisomer. Interestingly, in contrast to the earlier Diels−Alder study using 2,3-butadiene **27** (*see* Scheme 4), hydrolytic ring opening of the cycloaddition product to give the corresponding *N*-Boc methyl ketone **31** was not observed during this study. This observation suggests that the presence of the substituent α to the quaternary center is important for the hydrolytic stability of enecarbamates **48a−d**.

With synthetic access to the 6,6-spirocyclic ring system established, 2D NMR studies were undertaken to determine the relative stereochemistry of the adjacent quaternary and

Scheme 8. *N*-Acyl Iminium Diels−Alder Cycloaddition of 24a To Give Enecarbamates 48a−d



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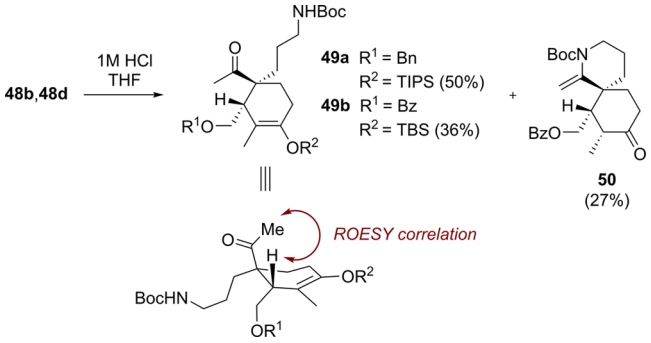
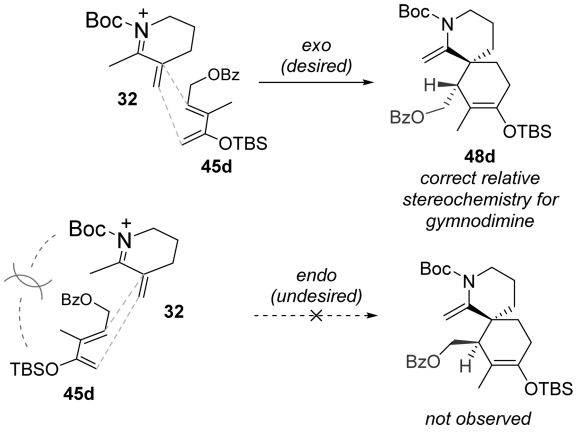
tertiary carbon centers. Disappointingly, however, no unambiguous correlations were able to be identified in the 2D NMR spectra of Diels–Alder products **48a–d**. Accordingly, hydrolysis of the benzoyl protected enecarbamates **48b** and **48d** was carried out, to afford methyl ketones **49a** and **49b** (Scheme 9).

Scheme 9. Hydrolysis of 6,6-Spirocyclic Enecarbamates 48b and 48d, and the Key 2D ROESY Correlation Observed for Methyl Ketones 49a and 49b



In the case of **48d**, some deprotection of the TBS enol ether also occurred, to give cyclic ketone **50**. We were pleased to observe a ROESY correlation between the methyl ketone protons and the cyclohexene ring methine in the 2D NMR spectrum of **49a** and **49b** that strongly suggested that these compounds possessed the relative stereochemistry corresponding to formal *exo* cycloaddition of *N*-Boc iminium **32** (Scheme 10).[10] This relative stereochemistry is the same as that possessed by the 6,6-spirocyclic imine found in the natural product gymnodimine **1**.

Scheme 10. Comparison of the Possible Transition States for the Diels–Alder Reaction of *N*-Boc Iminium Ion 32 and Diene 45d To Afford Exclusively the Formal *exo* Product 48d That Possesses the Correct Relative Stereochemistry for Gymnodimine 1



The origin of the *exo* selectivity of Diels–Alder cycloaddition of **32** and dienes **45** is not well understood at the present time. Catalytic Diels–Alder reactions of α-methylene lactams and lactones have generally been found to favor the *exo* products,[11] but how this is mechanistically related to the reaction of α,β-unsaturated *N*-acyl iminium ion **32** in the present study is unclear. It is possible that steric interactions between the *N*-Boc or **32** and the large 2-silyloxy substituent of dienes **45** would disfavor *endo* cycloaddition. Steric interactions with the additional methyl group in **32** with respect to previously investigated iminium ion **8** (see Scheme 1) might also play a role in the observed *exo* selectivity.

CONCLUSION

In summary, novel enecarbamate **24a** has been established as a convenient stable precursor for *in situ* generation of iminium ion **32**. In contrast to previously reported *N*-acyl iminium precursors, the multistep preparation was readily performed on a multigram scale and both ester **22** and methyl ether **24a** were found to be stable to storage. Generation of six-membered α,β-unsaturated *N*-Boc iminium ion **32** was found to proceed readily at low temperatures in the presence of Lewis and Brønsted acids. In contrast, use of the five-membered iminium precursor **27** was unproductive in these preliminary studies, due to facile hydrolysis and decomposition on storage or exposure to acid.

Six-membered iminium precursor **24a** was shown to undergo efficient Diels–Alder reaction with 2,3-dimethyl butadiene **29** in the presence of Lewis and Brønsted acids, with concomitant hydrolysis of the enecarbamate, to give cycloaddition product **34**. Conditions were also identified for the addition of nucleophiles to give both enecarbamate (**37**, **39**) and ring-opened (**40**) products.

Finally, the use of iminium precursor **24a** was extended to the Diels–Alder reaction with complex 2-silyloxy dienes **45a–d** for synthesis of 6,6-spirocyclic ring systems related to the spirocyclic imine fragment of gymnodimine **1**. The use of triethylamine to quench the reaction was found to be essential, to allow the successful isolation of 6,6-spirocyclic enecarbamates **48c** and **48d** in high yield. A key correlation observed in the 2D ROESY NMR spectrum of **49a** and **49b** allowed the stereochemical assignment of **48a–d** as products of a formal *exo* cycloaddition process, possessing the same relative stereochemistry as the corresponding 6,6-spirocyclic imine fragment of the natural product gymnodimine **1**. Further studies to probe the mechanism of the *N*-acyl iminium Diels–Alder reaction and application to natural product synthesis are underway and will be reported in due course.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in flame- or oven-dried glassware under a dry nitrogen atmosphere unless otherwise stated. CH_2Cl_2, $(CH_3)_2CO$, DMF, THF, CH_3CN, and Et_2O were obtained from a solvent purifier. All other reagents were used as received unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions performed at low temperature were cooled with either an acetone/dry ice bath to reach −78 °C, and an acetone/brine/dry ice bath to reach −30 °C, or a water ice bath to reach 0 °C. Flash chromatography was carried out using 0.063–0.1 mm silica gel with the required solvent system. TLC was carried out using 0.2 mm silica plates, and compounds were visualized using UV irradiation at 365 nm and/or staining with vanillin in methanolic sulfuric acid or potassium permanganate and potassium carbonate in aqueous sodium hydroxide. Melting points were measured with a hot–stage apparatus and are uncorrected. Infrared (IR) spectra were recorded as thin films. Absorption maxima are expressed in wavenumbers (cm^{-1}) and recorded using a range of 450–4000 cm^{-1}. NMR spectra were recorded as indicated on a spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. All chemical shifts are reported in ppm relative to tetramethylsilane (δ = 0 for ^{1}H NMR) and CDCl3 (δ = 77.0 for ^{13}C NMR). ^{1}H NMR data are reported as chemical shift, relative integral, multiplicity (s, singlet; d,

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doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet), coupling constant (*J*, Hz), and assignment, Assignments were made with the aid of COSY, NOESY, and HSQC experiments where required. High resolution mass spectra were recorded using a nominal accelerating voltage of 70 eV or on a TOF-Q mass spectrometer.

β-Ketoester ***20***. Ethyl acetoacetate **17** (3.42 g, 26.3 mmol, 1.5 equiv) was dissolved in acetone (50 mL) and K_2CO_3 (4.24 g, 30.7 mmol, 1.8 equiv) added, followed by iodide **19**[12] (5.00 g, 17.5 mmol, 1.0 equiv) and DMF (4 mL). The mixture was left to stir at rt for 48 h. The mixture was concentrated *in vacuo*, redissolved in EtOAc (100 mL), and washed with sat. NH_4Cl (75 mL) and then adjusted to pH 5 with 1 M HCl. The aqueous phase was extracted with EtOAc (3 × 40 mL), and the organic phases were washed with brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by chromatography (20−33% hexanes−EtOAc) to yield **20** as a clear oil (4.52 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): 4.59 (bs, 1H), 4.18 (dq, *J* = 7.2 Hz, 2H), 3.43 (t, *J* = 7 Hz, 1H), 3.11 (m, 2H), 2.21 (s, 3H), 1.84 (m, 2H), 1.52−1.37 (m, 11H), 1.26 (dt, *J* = 7 and 2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 203.0, 169.8, 156.1, 79.3, 61.5, 59.3, 40.1, 29.1, 28.5, 27.9, 25.2, 14.2; IR (film): 3369, 2976, 2931, 2874, 1736, 1705, 1518, 1450, 1391, 1366, 1249 cm^{-1}; HRMS: Calculated for $C_{14}H_{25}NO_5Na^+$ [M + Na]$^+$: 310.1637, found: 310.1625.

N-Boc Enecarbamate ***22***. To a solution of *β*-ketoester **20** (6.15 g, 21.4 mmol) in CH_2Cl_2 (12 mL) was added TFA (8 mL, 104 mmol, 4.9 equiv), and stirring continued at rt for 24 h. The mixture was concentrated *in vacuo*,k and sat. $NaHCO_3$ (120 mL) and EtOAc (80 mL) were added. The aqueous layer was adjusted to approximately pH 10−11 using potassium carbonate. The mixture was stirred for 3 h before separation of the layers and re-extraction of the aqueous layer using EtOAc (2 × 40 mL). The organic phases were washed with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield **21**[13] as a colorless solid. Data for *N*-H enecarbamate **21**. R_f 0.34 (hexanes−EtOAc 7:3); IR (film) ν_{max} 3344, 2975, 2938, 1659, 1578, 1528, 1367, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (s, 1H), 4.02−4.07 (q, *J* = 7.2 Hz, 2H), 3.12−3.14 (m, 2H), 2.30−2.33 (t, *J* = 6.0 Hz, 2H), 2.16 (s, 3H), 1.68−1.74 (q, *J* = 6.0 Hz, 2H), 1.18−1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.1, 153.1, 91.7, 58.6, 41.7, 22.7, 21.7, 21.5, 14.7; HRMS (ESI$^+$) Calculated for $C_9H_{15}NO_2Na^+$ [M + Na]$^+$: 192.0995, found 192.1003. The solid was dissolved in dry THF (30 mL) and cooled to 0 °C under N_2. To the mixture was added 60% NaH (940 mg, 23.6 mmol, 1.1 equiv) in portions. The mixture was left to stir for 10 min at 0 °C and 10 min at rt before being cooled to 0 °C. A solution of Boc_2O (5.84 g, 26.8 mmol, 1.3 equiv) in dry THF (20 mL) was added over the course of 30 min followed by addition of Et_3N (3.73 mL, 26.8 mmol, 1.3 equiv) and DMAP (520 mg, 4.28 mmol, 0.2 equiv). The mixture was stirred for 2 h at 0 °C and then for 18 h at rt. Another portion of Boc_2O (2.34 g, 10.7 mmol, 0.50 equiv) was added and the mixture was stirred for another 6 h at rt. The mixture was transferred to a separating funnel containing Et_2O (50 mL) and sat. NH_4Cl (100 mL). The aqueous layer was extracted with 50 mL of EtOAc. The organic phases were washed with sat. $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The mixture was purified by chromatography (5−10% EtOAc−hexanes) to afford **22** (4.78 g, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (2H, q, *J* = 7 Hz), 3.49−3.45 (2H, m), 2.34−2.28 (5H, m), 1.77−1.68 (2H, m), 1.44 (9H, s), 1.23 (3H, t, *J* = 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 168.4, 153.6, 147.7, 114.5, 81.4, 60.0, 44.7, 28.3, 24.7, 23.2, 21.9, 14.4; IR (film): 2978, 2938, 1702, 1608, 1453, 1364, 1337, 1303, 1241 cm^{-1}; HRMS: Calculated for $C_{14}H_{23}NO_4Na^+$ [M + Na]$^+$: 292.1519, found: 292.1527.

Alcohol ***23***. To a solution of ester **22** (1.12 g, 4.40 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added DIBAL-H (1.38 g, 9.69 mmol, 2.2 equiv) dropwise over 10 min. The solution was allowed to stir for 1 h at −78 °C before EtOAc (60 mL) and half-saturated potassium sodium tartrate (30 mL) were added. The solution was allowed to stir vigorously for 2 h before the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography afforded **23** (0.95 g, 95%) as a yellow oil. R_f 0.26 (hexanes−EtOAc, 3:1); IR (film) ν_{max} 3352, 2974, 2931, 1675, 1518, 1253, 1169 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.78 (s, 1H), 4.70 (s, 1H), 3.05 (q, *J* = 6.4 Hz, 2H), 2.29 (s, 3H), 2.24 (td, *J* = 8, 0.8 Hz, 2H), 1.52−1.59 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.8, 156.1, 148.4, 125.8, 79.1, 40.0, 29.0, 28.5, 27.8, 25.9; HRMS (ESI$^+$) calculated for $C_{12}H_{21}NO_3Na^+$[M + Na]$^+$: 250.1414, found 250.1423.

Methyl Ether ***24a***. To a solution of alcohol **23** (0.34 g, 1.48 mmol) in THF (20 mL) at 0 °C was added sodium hydride (60%, 0.15 g, 3.85 mmol, 2.6 equiv). The solution was warmed to rt and MeI (0.84 g, 5.94 mmol, 4.01 equiv) added. The reaction was heated to 45 °C for 19 h before cooling to rt and careful addition of H_2O (15 mL). The aqueous layer was extracted with 1:1 EtOAc−hexanes (3 × 20 mL) before the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over magnesium sulfate, and concentrated *in vacuo*. Purification by chromatography (EtOAc−hexanes, 20:80 + 0.25% Et_3N) afforded **24a** (0.29 g, 91%) as a yellow oil. R_f 0.28 (hexanes-EtOAc, 4:1); IR (film) ν_{max} 2975, 2930, 1696, 1658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 2H), 3.48−3.50 (m, 2H), 3.31 (s, 3H), 2.13 (td, *J* = 7.2, 1.6 Hz, 2H), 2.35 (t, *J* = 1.8 Hz, 3H), 1.74−1.80 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.2, 134.7, 119.5, 80.5, 72.6, 57.8, 44.7, 28.5, 26.1, 23.7, 18.3; HRMS (ESI$^+$) calculated for $C_{13}H_{23}NO_3Na^+$[M + Na]$^+$: 264.1570, found 264.1574.

TMS Ether ***24b***. To a solution of alcohol **23** (50 mg, 0.22 mmol) and Et_3N (55 *μ*L, 0.43 mmol, 2.0 equiv) in CH_2Cl_2 (2 mL) at 0 °C was added a solution of TMSCl (30 mg, 0.24 mmol, 1.1 equiv) in CH_2Cl_2 (0.3 mL) before stirring at rt for 3 h. The reaction was diluted with diethyl ether (10 mL), washed with saturated sodium bicarbonate (2 mL) and brine (2 mL), dried over magnesium sulfate, and concentrated *in vacuo* to afford **24b** (50 mg, 79%) as a colorless oil. R_f 0.61 (hexanes−EtOAc, 7:3); IR (film) ν_{max} 2923, 2854, 1699, 1337, 1139, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 2H), 3.47−3.50 (m, 2H), 2.01 (s, 3H), 1.48 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 158.1, 144.0, 122.0, 80.4, 62.8, 29.9, 28.6, 23.7, 0.2; HRMS (ESI$^+$) calculated for $C_{15}H_{29}NO_3SiNa^+$[M + Na]$^+$: 322.1809, found 322.1806.

N-Boc Enecarbamate Ester ***26***. To a solution of iodide **25**[12] (4.13 g, 15.2 mmol) in acetone (69 mL) was added K_2CO_3 (6.32 g, 45.7 mmol, 3.0 equiv), ethyl acetoacetate (2.90 mL, 22.8 mmol, 1.5 equiv), and DMF (3.5 mL). The mixture was stirred for 48 h, before being concentrated under reduced pressure, resuspended in EtOAc (80 mL), and diluted with sat. aq. NH_4Cl (40 mL). The pH was adjusted to 3 using 1 M HCl (ca. 50 mL), and the mixture was extracted with EtOAc (2 × 40 mL). The organic phases were washed with brine (40 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by chromatography (hexanes−EtOAc, 4:1) afforded the alkylkated *β*-ketoester (2.87 g, 69%) as a pale yellow oil: ν_{max}(neat) cm^{-1} 3379, 1712, 1624, 1388, 1366, 1237; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.61 (br s, 1H), 4.16−4.22 (m, 2H), 3.50 (t, *J* = 7.2 Hz, 1H), 3.10−3.14 (m, 2H), 2.24 (s, 3H), 1.96−2.05 (m, 2H), 1.31 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 202.8, 169.5, 155.9, 79.4, 61.6, 60.4, 57.0, 38.5, 29.3, 28.4, 14.1; HRMS (ESI +) calculated for $C_{13}H_{23}NO_5Na^+$ [M + Na]$^+$: 296.1468, found 296.1458. To a solution of the *β*-ketoester (3.29 g, 12.0 mmol) in CH_2Cl_2 (110 mL) were added PTSA (0.40 g, 2.10 mmol, 0.17 equiv) and silica (0.40 g), and the mixture was stirred for 2 h, then diluted with sat. aq. $NaHCO_3$ (70 mL), and extracted with EtOAc (2 × 40 mL). The organic phases were washed with brine (70 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by chromatography (hexanes−EtOAc, 9:1) afforded **26** (2.36 g, 77%) as a colorless solid. Mp 51−54 °C; ν_{max}(neat) cm^{-1} 3055, 2988, 1712, 1362, 1265, 1222; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.0 Hz, 2H), 3.75−3.80 (m, 2H), 2.66−2.71 (m, 2H), 2.39 (s, 3H), 1.32 (s, 9H), 1.08 (t, *J* = 7.0 Hz, 3H); δ_C (100 MHz, $CDCl_3$) δ 166.4, 155.3, 152.1, 108.9, 81.3, 59.5, 47.3, 28.3, 26.8, 14.5, 14.4; HRMS (ESI+) calculated for $C_{13}H_{21}NO_4Na^+$ [M + Na]$^+$: 278.1363, found 278.1353.

Alcohol ***27***. To a solution of ester **26** (0.35 g, 1.37 mmol, 1.0 mol equiv) in CH_2Cl_2 (5.5 mL) was added DIBAL-H (5.5 mL, 5.48 mmol, 4.0 equiv) at −78 °C, and the mixture stirred for 1.5 h before sat. Rochelle's salt solution (50 mL) was added. The mixture was warmed

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to rt before additional CH_2Cl_2 (50 mL) and sat. Rochelle's salt solution (50 mL) were added, and the solution was stirred at rt for 2 h. The phases were separated and extracted with EtOAc (2 × 50 mL) before the organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography (hexanes−EtOAc, 1:1 + 2% MeOH) afforded **27** (0.25 g, 86%) as a colorless oil. R_f 0.26 (hexane−EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (s, 2H), 3.72 (t, J = 9.4 Hz, 2H), 2.56 (t, J = 8.0 Hz, 2H), 2.10 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.7, 136.6, 117.0, 80.1, 58.8, 46.6, 28.5, 28.0, 13.1; HRMS (ESI+) calculated for $C_{11}H_{19}NO_3Na^+$ [M + Na]$^+$: 236.1257, found 236.1253.

Enone ***28***. R_f 0.32 (hexanes−EtOAc 3:1); IR (film) ν_{max} 3360, 2976, 2931, 1680, 1365, 1169 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.80 (s, 1H), 4.66 (s, 1H), 3.08 (q, J = 6.4 Hz, 2H), 2.31 (s, 3H), 2.26 (td, J = 8, 0.8 Hz, 2H), 1.54−1.62 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.0, 156.1, 148.4, 125.9, 79.2, 40.1, 29.0, 28.5, 27.8, 25.9; HRMS (ESI$^+$) calculated for $C_{12}H_{21}NO_3Na^+$ [M + Na]$^+$: 250.1414, found 250.1416.

β-Hydroxy ketone ***30***. On storage, alcohol **27** converted to **30**: R_f 0.30 (hexanes−EtOAc, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (br s, 1H), 3.76 (m, 2H), 3.14 (q, J = 7 Hz, 2H), 2.72 (pent, J = 6 Hz, 1H), 2.54 (br s, 1H), 2.21 (s, 3H), 1.86 (sext, J = 7 Hz, 1H), 1.66 (1H, sext, J = 7 Hz), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 156.2, 79.6, 62.7, 52.2, 38.6, 29.8, 28.5, 28.4; IR (film): 3373, 2977, 2933, 2882, 1693, 1524, 1454, 1392, 1366, 1275, 1251; HRMS (ESI$^+$) Calculated for $C_{11}H_{21}NO_4Na^+$ [M + Na]$^+$: 254.1363, found: 254.1374.

Enone ***31***. A sample of β-Hydroxy ketone **30** was stirred in dry CH_2Cl_2 at rt with $MgSO_4$ for 24 h. Filtration and concentration followed by chromatography afforded **31** as a colorless amorphous solid. Mp 33−37 °C; R_f 0.25 (hexane−EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.86 (s, 1H), 4.61 (br s, 1H), 3.21 (q, J = 6 Hz, 2H), 2.44 (t, J = 7 Hz, 2H), 2.34 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 156.1, 146.4, 127.1, 79.3, 39.8, 31.6, 28.5, 25.9; IR (film): 3365, 2977, 2932, 1682, 1520, 1447, 1392, 1366, 1273, 1250; HRMS (ESI$^+$) Calculated for $C_{11}H_{19}NO_3Na^+$ [M + Na]$^+$: 236.1257, found: 236.1264.

Diels−Alder Product ***34***. To a solution of alcohol **23** (240 mg, 1.07 mmol) and 2,3-butadiene **29** (0.5 mL, 4.28 mmol, 4.0 equiv) in CH_2Cl_2 (4 mL) at 0 °C was added TFA (80 μL, 1.0 equiv) and the reaction stirred for 18 h at rt. Et_2O (10 mL) and sat. $NaHCO_3$ (10 mL) were added and the aqueous phase extracted with EtOAc (10 mL). The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by chromatography (10−30% EtOAc in hexane) afforded **34** (142 mg, 43%) as a colorless oil. R_f 0.32 (hexane−EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (br s, 1H), 3.04 (q, J = 6 Hz, 2H), 2.29 (br d, J = 17 Hz, 1H,), 2.07 (s, 3H), 1.93−1.83 (m, 3H), 1.80 (br d, J = 17 Hz, 1H,), 1.61 (s, 3H), 1.60- 1.51 (m, 5H), 1.49−1.38 (m, 10H), 1.37−1.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.1, 156.1, 125.1, 123.6, 79.3, 50.7, 41.0, 39.0, 34.5, 29.9, 29.1, 28.5, 25.4, 25.1, 19.4, 18.8; IR (film): 3360, 2976, 2923, 2868, 1694, 1518, 1449, 1391, 1365, 1272, 1248; HRMS (ESI$^+$) Calculated for $C_{18}H_{31}NO_3Na^+$ [M + Na]$^+$: 332.2196, found: 332.2208.

Spirocyclic Imine ***35***. To a solution of Diels−Alder product **34** (100 mg, 0.32 mmol) in CH_2Cl_2 (2 mL) was added TFA (1.0 mL). The mixture was stirred at rt for 18 h before being concentrated *in vacuo*. The resultant oil was taken up in THF (5 mL) and NEt_3 (1 mL) and $MgSO_4$ (1.50 g) added and stirring continued at rt for 18 h. The mixture was filtered, concentrated *in vacuo* and purified by chromatography (EtOAc−MeOH−aq.NH_3 (90:9:1), silica column pre-eluted with the same solvent) to give **35** (49 mg, 79%) as a colorless oil. R_f 0.34 (EtOAc−MeOH−aq.NH_3, 90:9:1), TLC plate pre-eluted with the same solvent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (br d, J = 17 Hz, 1H), 3.40 (br d, J = 17 Hz, 1H), 2.25 (br d, J = 17 Hz, 1H,), 2.07 (m, 1H), 1.95 (dd, J = 2.0, 1.6 Hz, 3H), 1.94−1.85 (m, 2H), 1.75−1.65 (m, 2H,), 1.64−1.55 (m, 8H), 1.43−1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 124.4, 123.1, 49.9, 38.8, 38.3, 31.6, 28.8, 27.9, 22.7, 19.5, 19.2, 18.9; IR (film): 2993, 2923, 2854, 1777, 1645, 1441, 1373, 1335, 1291, 1248, 1228 cm^{-1}; HRMS (ESI$^+$) Calculated for $C_{13}H_{22}N$ [M]$^+$: 192.1747, found: 192.1748.

Furan Adduct ***37***. To a solution of methyl ether **24a** (100 mg, 0.414 mmol) in CH_2Cl_2 (2 mL) under nitrogen at −10 °C was added $Sc(OTf)_3$ (10 mg, 0.21 mmol, 5 mol %) followed by dropwise TMS furan (90 μL, 0.54 mmol, 1.3 equiv). The reaction was stirred at this temperature for 0.5 h before addition of sat. aqueous $NaHCO_3$ (10 mL), extracted with Et_2O (3 × 10 mL), and washed with brine (20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by chromatography (hexanes−EtOAc, 20:1 + 1% TEA) to give **37** (56 mg, 46%) as a colorless oil. IR (film) ν_{max} 2971, 1757, 1693, 1377, 1253, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (dd, J = 1.5, 5.6 Hz, 1H), 6.11 (dd, J = 1.9, 5.6 Hz, 1H), 5.10 (tt, J = 1.8, 7.0 Hz, 1H), 3.49−3.55 (m, 1H), 3.36−3.42 (m, 1H), 2.38−2.49 (m, 2H), 2.00−2.14 (m, 1H), 1.95 (t, J = 1.9 Hz, 1H), 1.73−1.79 (m, 2H), 1.49 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 156.1, 154.0, 134.1, 121.6, 116.6, 82.4, 80.5, 44.5, 37.0, 28.4, 23.9, 18.7; HRMS (ESI+) calculated for C16H23NO4Na+ [M + Na]+: 316.1519, found 316.1511.

N-Methylindole Adducts ***39*** *and* ***40***. To a solution of methyl ether **24a** (100 mg, 0.41 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added $Sc(OTf)_3$ (10 mg, 0.21 mmol, 5 mol %) at −10 °C. The solution was stirred for 5 min before *N*-methylindole (55 μL, 0.435 mmol, 1.1 equiv) was added. The mixture was quenched with aqueous sat. $NaHCO_3$ (10 mL) after 3 h, extracted with Et_2O (3 × 10 mL), and washed with brine (20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The crude oil was purified by chromatography (hexanes−EtOAc, 20:1 + 1% Et_3N) to give **39** (44 mg, 32%) and **40** (65 mg, 44%) as colorless oils. Cyclic enecarbamate **39**: IR (film) ν_{max} 2980, 1687, 1471, 1366, 1251, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.18−7.22 (m, 1H), 7.05−7.10 (m, 1H), 6.78 (s, 1H), 3.71 (s, 3H), 3.48−3.51 (m, 2H), 3.45 (s, 2H), 2.15 (s, 3H), 2.03 (t, J = 6.7 Hz, 2H), 1.66−1.74 (m, 2H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 137.3, 130.6, 128.1, 126.6, 122.3, 121.6, 119.1, 118.7, 112.8, 109.2, 80.1, 30.4, 44.7, 32.7, 28.6, 28.5, 27.3, 24.2, 18.7; HRMS (ESI$^+$) calculated for $C_{21}H_{28}N_2O_2Na^+$ [M + Na]$^+$: 363.2043, found 363.2032. Ring-opened adduct **40**: IR (film) ν_{max} 3364, 2980, 1702, 1510, 1365, 1250, 1147, 1090, 801, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.58 (td, J = 1.0, 7.6 Hz, 1H), 7.09−7.13 (m, 1H), 6.80 (s, 1H), 4.50 (br s, 1 H), 3.73 (s, 3H), 3.06−3.09 (m, 1H), 3.00−3.05 (m, 2H), 3.03 (dd, J = 8.1, 14.0 Hz, 1H), 2.90−2.97 (m, 1H), 2.82 (dd, J = 6.0, 14.0 Hz, 1H), 2.02 (s, 3H), 1.66−1.75 (m, 1H), 1.52−1.56 (m, 1H), 1.47−1.50 (m, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.6, 137.0, 129.3, 127.7, 127.0, 121.6, 118.9, 118.7, 111.8, 109.2, 79.2, 53.2, 40.5, 32.6, 30.0, 28.8, 28.4, 28.0; HRMS (ESI$^+$) calculated for $C_{21}H_{30}N_2O_3Na^+$[M + Na]$^+$: 381.2149, found 381.2139.

General HWE Procedure for Ketones 44, 46a, and 46b. To a solution of phosphonate **42** or **43** (1.0 equiv) in THF (5 mL, 0.4 M) was added NaH (1.1 equiv) portionwise at 0 °C. The mixture was stirred for 10 min before a solution of aldehyde **41a**[14] or **41b**[15] (1.0 equiv) in THF (2 mL) was added dropwise. After stirring for 3 h the reaction was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes−EtOAc, 8:1) afforded the ketone products.

OBn Ketone ***44***.[16] (200 mg, 65%). IR (film) ν_{max} 3032, 2854, 1675, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.34 (m, 5H), 6.80 (dt, J = 4.4, 15.9 Hz, 1H), 6.35 (dt, J = 1.9, 15.9 Hz, 1H), 4.58 (s, 2H), 4.21 (dd, J = 1.9, 4.4 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.3, 143.1, 137.8, 130.5, 128.7, 128.1, 127.9, 73.1, 69.0, 27.5. HRMS (ESI$^+$) calculated for $C_{12}H_{14}O_2Na^+$ [M + Na]$^+$: 213.0883, found 213.0881.

OBn 3-Me Ketone ***46a***. (1.3 g, 67%). IR (film) ν_{max} 3070, 2931, 1714, 1585, 1205, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29−7.38 (m, 5 H), 6.70 (tq, J = 1.2, 5.6 Hz, 1 H), 4.57 (s, 2 H), 4.26−4.28 (m, 2 H), 2.31 (s, 3 H), 1.73−1.74 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.4, 139.6, 138.1, 137.8, 128.7, 128.1, 128.0, 73.3, 67.5,

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31.0, 25.5, 11.6; HRMS (ESI$^+$) calculated for $C_{13}H_{16}O_2Na^+$ [M + Na]$^+$: 227.1043, found 227.1045.

OBz 3-Me Ketone ***46b***. (334 mg, 64%). Mp 80−81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06−8.09 (m, 2H), 7.57−7.61 (m, 1H), 7.45−7.48 (m, 2H), 6.72 (tq, J = 1.2, 5.9 Hz, 1H), 5.07 (dd, J = 1.0, 5.9 Hz, 2H), 2.36 (s, 3H), 1.89 (d, J = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.2, 166.2, 139.6, 135.9, 133.4, 129.8, 128.6, 61.9, 25.7, 11.8. Data were in agreement with those previously reported in the literature.[17]

General Procedure for 2-Silyloxy Dienes 45a−d. To a solution of ketone in THF (6 mL, 0.15 M) were added TEA (2.4 equiv) and the appropriate silyl triflate (1.2 equiv) at 0 °C. The solution was stirred for 1 h before the addition of sat. aq. $NaHCO_3$ (20 mL) and extraction with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by chromatography (hexanes−EtOAc, 9:1 + 0.25% TEA) afforded the 2-silyloxy diene products.

TIPS 3-H OBn Diene ***45a***. (0.32 g, 76%). R_f 0.58 (hexanes−EtOAc, 19:1); IR (film) ν_{max} 2941, 2866, 1724, 1461, 1318, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.35 (m, 5H,), 6.09−6.18 (m, 2H), 4.53 (s, 2H), 4.29 (d, J = 17.6 Hz, 2H), 4.11 (d, J = 2.4 Hz, 2H), 1.22−1.29 (m, 5H), 1.12 (s, 18); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.7, 125.7−130.2, 128.1, 127.8, 94.9, 72.1, 70.0, 18.0, 12.6; HRMS (ESI+) calculated for $C_{21}H_{34}O_2SiNa^+$ [M + Na]$^+$: 369.2220, found 369.2225.

TIPS 3-Me OBn Diene ***45b***. (210 mg, 78%). IR (film) ν_{max} 2942, 2866, 1593, 1335, 1293, 1146, 1065, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28−7.35 (m, 5H), 6.28 (t, J = 6.6 Hz, 1H), 4.52 (s, 2H), 4.45 (s, 1H), 4.31 (s, 1H), 4.19 (d, J = 6.6 Hz, 2H), 4.11 (d, J = 2.4 Hz, 2H), 1.77 (s, 3H), 1.23−1.29 (m, 3H), 1.11−1.13 (m, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.2, 124.4−138.6, 128.5, 127.9, 91.3, 72.1, 67.0, 18.3, 13.0; HRMS (ESI+) calculated for $C_{22}H_{36}O_2SiNa$+ [M + Na]+: 383.2377 found 383.2385.

TIPS 3-Me OBz Diene ***45c***. (360 mg, 95%). IR (film) ν_{max} 2942, 2863, 1462, 1250, 1104, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03−8.08 (m, 2H), 7.53−7.57 (m, 1H), 7.41−7.47 (m, 2H), 6.32 (t, J = 7.0 Hz, 1H), 4.98 (d, J = 7.0 Hz, 2H), 4.53 (d, J = 1.3 Hz, 1H), 4.38 (d, J = 1.3 Hz, 1H), 1.90 (s, 3H), 1.10−1.12 (m, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 156.9, 135.9, 133.0, 130.5, 129.7, 128.5, 121.5, 92.3, 62.2, 18.2, 17.9, 13.8, 12.9; HRMS (ESI$^+$) calculated for $C_{22}H_{34}O_3SiNa^+$ [M + Na]$^+$: 397.2169, found 397.2165.

TBS 3-Me OBz Diene ***45d***. (270 mg, 98%). IR (film) ν_{max} 1718, 1674, 1451, 1268, 1177, 1113, 1070, 1027, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03−8.05 (m, 2H), 7.55−7.57 (m, 1H), 7.42−7.45 (m, 2H), 6.22−6.26 (m, 1H), 4.97 (d, J = 7.0 Hz, 2H), 4.56 (s, 1H), 4.37 (s, 1H), 1.89 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 156.5, 135.8, 132.9, 130.4, 129.6, 128.3, 121.4, 93.2, 62.0, 25.9, 25.7, 18.3, 18.1, 13.6, −4.6; HRMS (ESI$^+$) calculated for $C_{19}H_{28}O_3SiNa^+$ [M + Na]$^+$: 355.1700, found 355.1690.

General Procedure for *α,β*-Unsaturated *N*-Acyl Iminium Diels−Alder Cycloaddition. To a solution of methyl ether **24a** (1.0 equiv) in CH_2Cl_2 (2 mL, ca. 0.5 M) at −78 °C was added $BF_3{\cdot}Et_2O$ (1.4 equiv) followed by a solution of the appropriate diene **45a−d** (1.0 equiv) in CH_2Cl_2 (1 mL) dropwise. The reaction was stirred for 0.5 h at this temperature before the addition of aq. sat. $NaHCO_3$ (10 mL) was added, extracted with Et_2O (3× 10 mL), and washed with brine (20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. Purification by chromatography (hexanes−EtOAc 25:1 + 1% TEA) afforded the 6,6-spirocyclic enecarbamate products.

TIPS OBn 6,6-Spirocyclic Enecarbamate ***48a***. (3 mg, 3%). R_f 0.47 (hexanes−EtOAc, 9:1); IR (film) ν_{max} 2932, 2864, 1694, 1459, 1373, 1194, 1149, 882 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.31 (5H, m), 5.09 (1H, dd, J = 5.9, 1.2 Hz), 4.92 (2H, s), 4.38−4.49 (2H, abq), 4.09−4.13 (1H, m), 3.88−3.91 (1H, dd, J = 8.0, 4.0 Hz), 3.23−3.28 (1H, dd, J = 9.9, 8.5 Hz), 2.87−2.94 (1H, td, J = 12.1, 3.4 Hz), 2.58−2.61 (1H, m), 2.14−2.19 (1H, m), 2.06−2.13 (2H, m), 1.93−2.00 (1H, m), 1.76−1.88 (1H, m), 1.49−1.53 (1H, m), 1.47 (9H, s), 1.39−1.44 (1H, m), 1.14−1.18 (1H, m), 1.12−1.20 (3H, m), 1.06−1.08 (18H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.2, 149.3, 139.1, 127.4−128.4, 107.8, 104.9, 80.0, 74.7, 73.5, 46.9, 39.3, 38.0, 33.6, 29.4, 28.6, 26.9, 21.0, 18.2, 12.8; HRMS (ESI$^+$) calculated for $C_{33}H_{53}NO_4SiNa^+$ [M + Na]$^+$: 578.3636, found 578.3617.

TIPS OBn 6,6-Spirocyclic Enecarbamate ***48b***. (70 mg, 34%). R_f 0.26 (hexanes−EtOAc, 19:1); IR (film) ν_{max} 2935, 2866, 1692, 1380, 1365, 1242, 1147, 1097, 882, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.28 (5H, m), 4.95−4.96 (2H, d, J = 6.7 Hz), 4.41 (2H, s), 4.15−4.20 (1H, m), 3.78−3.81 (1H, dd, J = 9.0, 3.1 Hz), 3.57−3.61 (1H, m), 2.82−2.89 (1H, td, J = 12.3, 3.5 Hz), 2.34−2.35 (1H, m), 2.17−2.22 (2H, m), 2.13−2.15 (1H, m), 2.06−2.10 (1H, m), 1.77−1.85 (1H, m), 1.75 (3H, s), 1.48−1.51 (1H, m), 1.46 (9H, s), 1.32−1.40 (1H, m), 1.16−1.26 (3H, m), 1.04−1.06 (18H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 151.0, 143.0, 139.4, 127.2−128.2, 111.3, 107.8, 80.0, 73.3, 73.0, 47.1, 39.3, 38.0, 33.8, 29.6, 28.6, 27.4, 21.1, 18.2, 17.2, 13.4; HRMS (ESI$^+$) calculated for $C_{34}H_{55}NO_4SiK^+$ [M + K]$^+$: 608.3532, found 608.3537.

TIPS OBz 6,6-Spirocyclic Enecarbamate ***48c***. (425 mg, 76%). IR (film) ν_{max} 2943, 2867, 1719, 1693, 1377, 1242, 1148, 1097, 882, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98−8.00 (m, 2H), 7.52−7.55 (m, 1H), 7.40−7.43 (m, 2H), 4.99 (d, J = 16.9 Hz, 2H), 4.69 (dd, J = 3.1, 11.0 Hz, 1H), 4.37 (dd, J = 6.3, 11.0 Hz, 1H), 4.27 (d, J = 12.3 Hz, 1H), 2.85 (td, J = 3.5, 12.3 Hz, 1H), 2.58 (s, 1H), 2.20−2.26 (m, 2H), 2.14 (dt, J = 3.1, 13.1 Hz, 1H), 1.80−1.88 (m, 1H), 1.77 (s, 3H), 1.52−1.57 (m, 1H), 1.41 (s, 9H), 1.18−1.25 (m, 1H), 1.01−1.04 (m, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 154.3, 150.4, 143.7, 132.6, 130.7, 129.5, 128.3, 109.7, 108.5, 80.2, 67.6, 46.7, 42.5, 40.6, 33.6, 29.3, 28.2, 27.2, 21.0, 18.1, 17.1, 13.2; HRMS (ESI$^+$) calculated for $C_{34}H_{53}NO_5SiNa^+$ [M + Na]$^+$: 606.3599, found 606.3600.

TBS OBz 6,6-Spirocyclic Enecarbamate ***48d***. (335 mg, 75%). IR (film) ν_{max} 2980, 1697, 1380, 1365, 1270, 1163, 1110, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97−8.00 (m, 2H), 7.50−7.54 (m, 1H), 7.39−7.43 (m, 2H), 4.98 (d, J = 16.6 Hz, 2H), 4.68 (dd, J = 3.1, 11.1 Hz, 1H), 4.40 (dd, J = 5.8, 11.1 Hz, 1H), 4.25 (d, J = 12.4 Hz, 1H), 2.84 (td, J = 3.5, 12.3 Hz, 1H), 2.55 (s, 1H), 2.20−2.25 (m, 1H), 2.12−2.16 (m, 2H), 2.05−2.09 (m, 1H), 1.75−1.82 (m, 1H), 1.71 (s, 3H), 1.49−1.54 (m, 1H), 1.45−1.46 (m, 1H), 1.41 (s, 9H), 1.17−1.22 (m, 1 H), 0.89 (s, 9 H), 0.03 (d, J = 3.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 154.3, 150.3, 143.7, 132.7, 130.7, 129.5, 128.3, 110.3, 108.6, 80.3, 67.1, 46.7, 42.6, 40.7, 33.6, 29.2, 28.3, 27.0, 25.8, 21.0, 18.2, 16.9, −3.8; HRMS (ESI$^+$) calculated for $C_{31}H_{47}NO_5SiNa^+$ [M + Na]$^+$: 564.3116, found 564.3131.

TIPS Methyl Ketone ***49a***. 6,6-Spirocyclic enecarbamate **48b** (20 mg, 0.03 mmol) was dissolved in tetrahydrofuran (3 mL) and water (2 mL), and 1 M HCl (2 mL) were added. The reaction was stirred for 48 h before being diluted with 1:1 EtOAc−hexanes (10 mL), and the organic phase was washed with saturated sodium bicarbonate (10 mL) and brine (10 mL), dried over sodium sulfate, and concentrated *in vacuo*. Purification by chromatography (hexanes−EtOAc, 80:20 + 1% Et_3N) afforded **49a** (10 mg, 50%) as a colorless oil. R_f 0.22 (hexanes−EtOAc, 4:1); IR (film) ν_{max} 2938, 1712, 1593, 1491, 1210, 933, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.36 (5H, m), 4.26−4.28 (2H, dd, J = 19.2, 11.6 Hz), 3.38−3.41 (1H, dd, J = 9.9, 3.0 Hz), 3.14−3.19 (1H, m), 3.05−3.07 (2H, m), 2.34−2.36 (1H, m), 2.07 (3H, s), 1.94−1.99 (2H, m), 1.78−1.86 (1H, td, J = 9.0, 5.0 Hz), 1.67 (3H, s), 1.63−1.65, (1H, m), 1.49−1.57 (1H, td, J = 12.9, 4.0 Hz), 1.42 (9H, s), 1.35−1.39 (2H, m), 1.23−1.27 (3H, m), 1.11−1.12 (1H, m), 1.04−1.06 (18H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 212.6, 156.0, 144.6, 128.1−138.0, 108.5, 79.3, 73.3, 71.1, 51.8, 50.2, 41.0, 30.6, 28.5, 26.9, 25.2, 21.2, 18.2, 16.6, 14.3, 13.3; HRMS (ESI$^+$) calculated for $C_{34}H_{57}NO_5SiNa^+$ [M + Na]$^+$: 610.3898, found 610.3893.

TBS Methyl Ketone ***49b***. To a solution of 6,6-spirocyclic enecarbamate **48d** (175 mg, 0.3 mmol) in THF (4 mL) was added 1 M HCl (2 mL) at 0 °C. The reaction was stirred at rt overnight and then diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by chromatography (hexanes−EtOAc, 3:1 + 1% TEA) to give **49b** (65 mg, 36%) and **50** (37 mg, 27%) as light yellow oils. Methyl ketone **48b**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95−7.97 (m, 2H), 7.53−7.56 (m, 1H), 7.41−7.44 (m, 2H), 4.53 (br s, 1H), 4.31 (dd, J = 3.4, 12.0 Hz, 1H), 4.10 (dd, J = 7.9, 12.0 Hz, 1H), 3.07−3.08 (m, 2H), 2.52 (d, J = 6.1 Hz, 1H), 2.10 (s, 3H), 2.06−2.07

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(m, 1H), 2.03−2.06 (m, 1H), 1.94−1.98 (m, 1H), 1.79−1.83 (m, 1H), 1.75−1.77 (m, 3H), 1.72−1.73 (m, 1H), 1.58 (td, J = 3.5, 13.2 Hz, 1H), 1.42 (s, 9H), 1.37−1.39 (m, 1H), 1.13−1.16 (m, 1H), 0.94 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.2, 145.1, 133.0, 130.0, 129.6, 128.4, 108.0, 64.9, 52.0, 48.7, 44.3, 30.9, 30.5, 30.3, 28.4, 26.9, 26.7, 21.2, 18.1, 16.4, 13.2, −0.1, −5.7. HRMS (ESI$^+$) calculated for $C_{31}H_{49}NO_6SiNa^+$ [M + Na]$^+$: 582.2903, found 582.2896. Cyclic ketone **50**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87−7.88 (m, 2H), 7.52−7.58 (m, 1H), 7.42−7.47 (m, 2H), 5.02 (s, 2H), 4.74 (dd, J = 2.1, 12.3 Hz, 1H), 4.35−4.36 (m, 1H), 4.29−4.33 (m, 1H), 2.93 (td, J = 3.9, 12.0 Hz, 1H), 2.73−2.82 (m, 1H), 2.54−2.58 (m, 1H), 2.52−2.54 (m, 2H), 2.49−2.52 (m, 1H), 2.3.1−2.42 (m, 1H), 2.82−2.93 (m, 1H), 1.70−1.76 (m, 1H), 1.63−1.70 (m, 1H), 1.53−1.58 (m, 1H), 1.47 (s, 9H), 1.18 (d, J = 6.8 Hz, 3H); HRMS (ESI$^+$) calculated for $C_{25}H_{33}NO_5Na^+$ [M + Na]$^+$: 450.2251, found 450.2255.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01343.

Copies of ^{1}H and ^{13}C NMR spectra for all compounds synthesized (PDF)

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