

Cleavage of a chiral auxiliary using RCM on an especially sterically crowded alkene: Syntheses of chiral carbo- and heterocycles

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Abstract

Chiral 1,5-, 1,6-, and 1,7-dienes generated in 3–4 steps from chiral auxiliary *p*-menthane-3-carboxaldehyde undergo RCM with notable discrepancies in reactivity depending on the nature and number of substituents flanking the central double bond. The chiral auxiliary is thus cleaved releasing a carbo- or heterocycle in the process. Special features concerning the RCM on these especially crowded systems are discussed.

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1. Introduction

From an organic synthesis standpoint, the ring-closing alkene metathesis reaction (RCM) has undergone a formidable evolution over a very short period of time: a barely known and little-used reaction just over 15 years ago, practicing synthetic organic chemists have resurrected this transformation in such a way that it quickly entered the league of the most powerful synthetic tools now available [1]. In fact, it has been a while since such excitement was seen in the synthetic community over an organic transformation. The advent of the well-defined ruthenium-based catalysts that are active, selective, and functional-group tolerant is largely responsible for the current popularity of RCM [2]. It is likely that RCM will continue to grow, perhaps at a slower pace now, as chemists use and study it and discover new ways to unleash its power.

Thrust forward by the discovery of Shrock's molybdenum and Grubb's ruthenium catalysts, several research groups made important contributions to the development

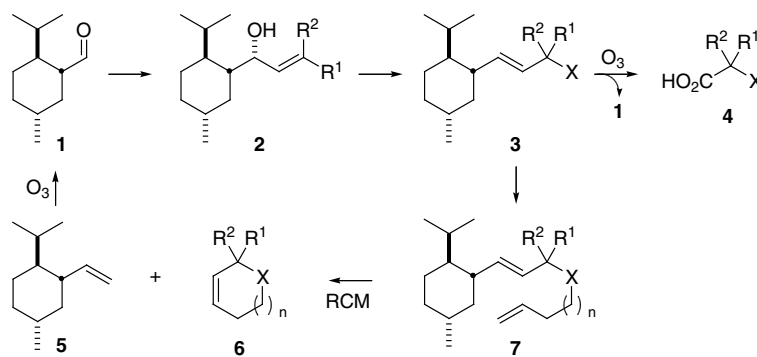
of new and more active catalysts [3]. Meanwhile, synthetic chemists were busy making rings of all sorts and sizes with these catalysts. Notably, heterocycles containing nitrogen [4,5], oxygen [5], silicon [1f], and phosphorus [6] were all found to be efficiently prepared by RCM. Sulfur-containing heterocycles remain a challenge, to this day [6].

In the last several years, we have elaborated several reaction sequences, all starting from *p*-menthane-3-carboxaldehyde **1**, that leads to chiral non-racemic α -substituted carboxylic acids (**4**), including amino acids (**4**, X = NR₂), upon oxidative cleavage of the auxiliary (Scheme 1). We realized that the sequence could lead directly to carbo- or heterocycles (**6**, X = C, O, N, S) if the auxiliary in **7** could be cleaved by RCM. The chiral auxiliary **1** would be recyclable via a simple ozonolysis of **5**. We report herein a full account of this work with an emphasis on the RCM cleavage in view of this special issue of the journal. The present work includes the synthesis of several new carbo- and heterocycles [7].

2. Results and discussion

At the onset, the internal double bond in **7**, especially in compounds bearing a quaternary allylic carbon (X, R¹ and

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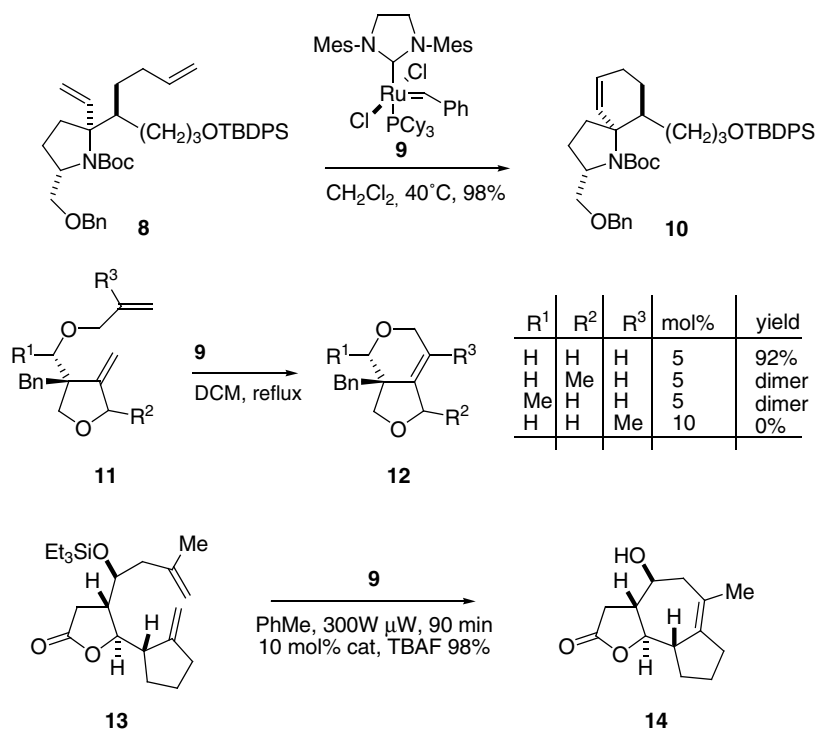
Scheme 1.

$R^2 \neq H$), did not look amenable to RCM. The double bond substituted with the voluminous menthyl fragment on one side and a tertiary or quaternary chiral carbon on the other side represents a serious deterrent to trying such a strategy.

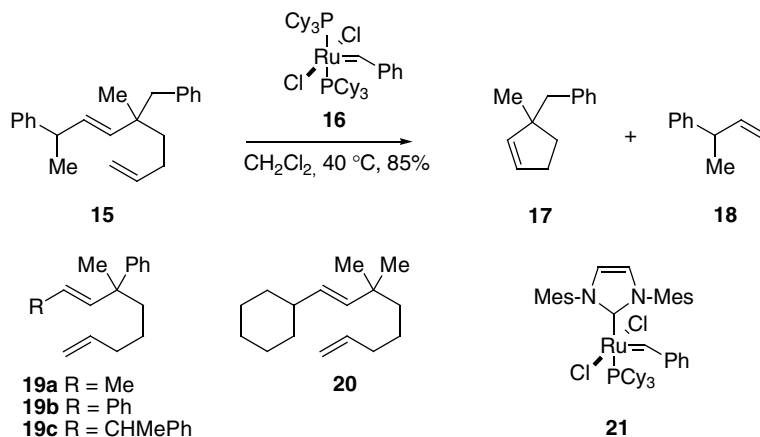
The vast majority of RCM reported in the literature involve two terminal double bonds and examples of RCM involving an internal alkene substituted at both allylic positions are rare as are examples of allylic quaternary carbons next to an internal or terminal alkene [1,8]. Scheme 2 provides selected examples. The center example is perhaps closer to our own work in that it clearly shows the detrimental effect (presumably for steric reasons) of substituents around the diene framework on the formation of dihydropyrans **12** [9]. Thomas and co-workers have shown that the presence of a *gem*-dimethyl group at the allylic position of a terminal double bond shuts

down a metathetic macrocyclization (not shown) [10]. A difficult RCM was successfully achieved from **13** by microwave irradiation as well as N_2 sparging to remove ethylene (Scheme 2, bottom) [11]. Generally, the second generation Grubbs (**9**) or Nolan catalysts (**21**, cf. Scheme 3) have contributed a great deal to widening the scope of the RCM towards making congested double bonds [3a,3b,12].

Exploratory experiments were conducted to replace *p*-menthane-3-carboxaldehyde **1** by another, less voluminous, aldehyde in order to increase our chances of terminating the sequence by a RCM reaction (cf. general sequence in Scheme 1). However, smaller auxiliaries caused problems because the steric bulk of the menthyl nucleus actually serves to make several transformations from **2** to **3** highly regioselective (i.e. with transposition of the double bond), be they displacement or rearrangement reactions [13]. So,



Scheme 2.



Scheme 3.

in order to gauge the consequence of the steric volume at the allylic positions on the diene, we effected RCM reactions on a series of racemic substrates **15**, **19**, and **20** (Scheme 3). Cyclopentene **17** was formed in 85% yield using Grubbs' first generation catalyst **16**, a very encouraging result. Likewise, substrates **19a** and **19b** gave the corresponding cyclohexene (>95% conversion by NMR) using catalyst **9** or **21** in refluxing 1,2-dichloroethane under high dilution (0.0005 M) for four days. Clearly, the presence of the quaternary carbon next to the alkene alone is enough to slow significantly the cyclization rate in the case of six membered rings. Discouragingly, substrates **19c** and **20** did not undergo a ring-closing metathesis using several different catalysts and under a wide range of reaction conditions. This did not bode well as any chiral auxiliary would have to possess at least a secondary carbon. Hope remained, nonetheless, as the formation of the cyclopentenes from **15** proceeded quite well with Grubbs' first generation catalyst **16**. The difference in reactivity between **15** and **19c** foretold of a trend of dramatically higher cyclization rate in the formation of five over six membered rings in this system (vide infra).

Our first attempts were aimed at the generation of carbocycles **24** from dienes **23**, themselves made from the highly stereoselective (>99%) addition of 1-pentenyl- or 1-butenylcuprate to the diastereomerically pure pivalate esters of **22** (Table 1) [7,13a]. We were astonished to find that the RCM reaction on molecules like **23a–d** actually proceeded quite well to give the corresponding cycloalkenes **24a–d** in high yield [7]. We surveyed a large number of catalysts and reaction conditions [3]. Although, Grubbs' first generation catalyst **16** could effect the cyclization in one case (entry 1), the Nolan catalyst **21** (or the similar Grubbs' second generation catalyst **9**) were consistently giving higher yields than all of the other ones we surveyed. We repeated each sequence of reaction shown in Table 1 with the diastereomer of **22**, or independently prepared the racemic carbocycle **24**, in order to ascertain the enantiomeric purity of the carbocycles **24**. This is because a Ru-catalyzed migration of the double bond around the ring

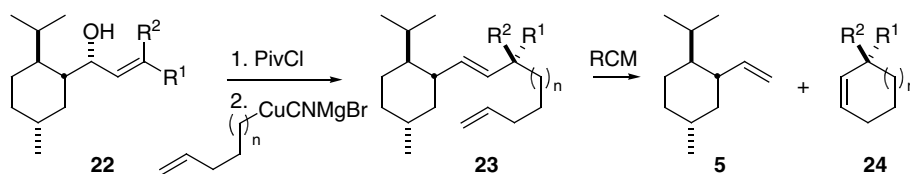
would be otherwise undetected since it leads to the enantiomer of **24**.

Notably, compounds **23e,g** possessing a chiral quaternary carbon required much harsher conditions (entries 6 and 8). Increasing dilution did not give satisfactory results in these cases. The most effective method to increase yields was to increase catalyst loading and use normal concentration and higher temperatures [14]. Cyclohexene **24f** possessing a quaternary carbon atom could not be prepared by RCM (entry 7). We tried a large number of catalysts and reaction conditions but it seemed that we had reached the limit as far as the generation of these carbocycles by RCM is concerned. The dimer of **23f** was the major isolated product in most cases. Microwave heating did not improve yields. Inert gas sparging [11] would not make any difference as ethylene or other volatile alkenes are never produced except in unwanted metatheses. The difference in reactivity between **23e** and **23f** is perhaps the most dramatic example of the kinetic preference for five-membered over six-membered ring formation in RCM [15]. This preference has been noted in a few instances but never with such conclusiveness [16].

Yet, the RCM reaction was very efficient for dienes **23b,d** giving cyclohexenes **24b,d** having a tertiary chiral center (entries 3 and 5). As low as 1 mol% of catalyst **21** was enough to effect the reaction. It seems that the addition of a single alkyl group ($R^1, R^2 \neq H$) adjacent to the alkene is enough to drastically reduce the reaction rate or even shut the reaction down (compare entries 2 vs. 6 and 3 vs. 7). Clearly, the initiation of the reaction at the terminal double bond could not be the issue here, thus the added steric volume near the reacting alkene must be the culprit. It overwhelms any beneficial consequence of a Thorpe–Ingold effect [17] brought about by the *gem* disubstitution.

Paradoxically, although the voluminous menthyl fragment undoubtedly slows the rate of cyclization (k_c in Scheme 4), it may nonetheless be partly responsible for the success of this transformation in general. The catalytic cycle is initiated by the reaction between the active form of the catalyst and the terminal alkene in **23** to give

Table 1
Yields of cycloalkenes **24** from the RCM of **23** using optimized conditions



Entry	23	R ¹	R ²	<i>N</i>	24	Cat. (mol%)	Yield 24 ^{c,d} (%)
1	23a	Bn	H	0	24a	16 (10) ^a	85
2	23a	Bn	H	0	24a	21 (1) ^b	81
3	23b	Bn	H	1	24b	21 (1) ^b	84
4	23c	TBSOCH ₂	H	0	24c	21 (1) ^b	87
5	23d	TBSOCH ₂	H	1	24d	21 (1) ^b	73
6	23e	Bn	Me	0	24e	21 (30) ^a	79 ^c
7	23f	Bn	Me	1	24f	21 (30) ^a	0
8	23g	TBSO(CH ₂) ₄	Me	0	24g	21 (30) ^a	70 ^c

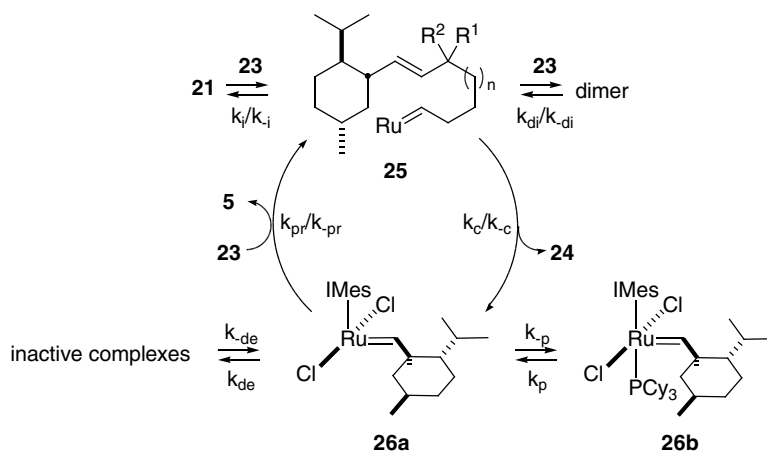
^a Conditions: ClCH₂CH₂Cl (0.01–0.002 M), reflux, 3 h.

^b CH₂Cl₂ (0.01–0.002 M), reflux, 3 h.

^c Isolated yield of **24** after flash chromatography.

^d ee's >98%.

^e See text.

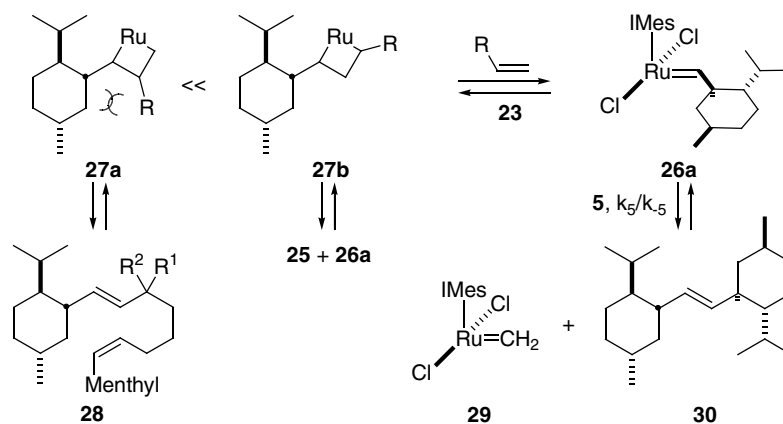


Scheme 4.

alkylidene **25**. When the latter cyclizes, it gives the desired product **24** and a new alkylidene **26a**. We believe that the propagating alkylidene **26a**, with a uniquely bulky alkylidene portion, plays several important roles: (a) recombination with phosphine is slow (low k_p) to give the inactive form **26b**, which must release phosphine before re-entering the catalytic cycle (Scheme 4) [18,19]; (b) **26a** may decompose more slowly (low k_{de}) than less bulky ruthenium alkylidenes to give inactive (or damaging) ruthenium complexes. This allows us to carry out the reactions for longer periods of time and at higher temperature [18]; (c) the steric bulk of **26a** also slows reactions with any compound relative to **23** (k_{pr}) (compound **24** (k_c) or compound **5** (k_s , Scheme 5) for example, i.e. differences in reaction rates are increased); (d) lastly, the bulk of the menthyl fragment strongly favors the forma-

tion of productive regioisomers **27b**, which contributes to the overall efficiency of the catalytic cycle (Scheme 5). Compound **28**, if produced via **27a**, would probably never re-enter the catalytic cycle because of its two highly substituted double bonds.

Other side reactions, such as double bond migration, were not a problem except in the worst cases (**23e–g**). The increased stability of the propagating catalyst **26a** helps by slowing down the generation of metal hydrides or other complexes that are thought to be responsible for such side reactions [1f,20]. Note that these characteristics are unique to our system. Using bulky ruthenium alkylidene similar to **26a** to initiate an RCM on a substrate having two crowded terminal double bonds, for example, would not help since the propagating species would be the ruthenium methylidene **29**.



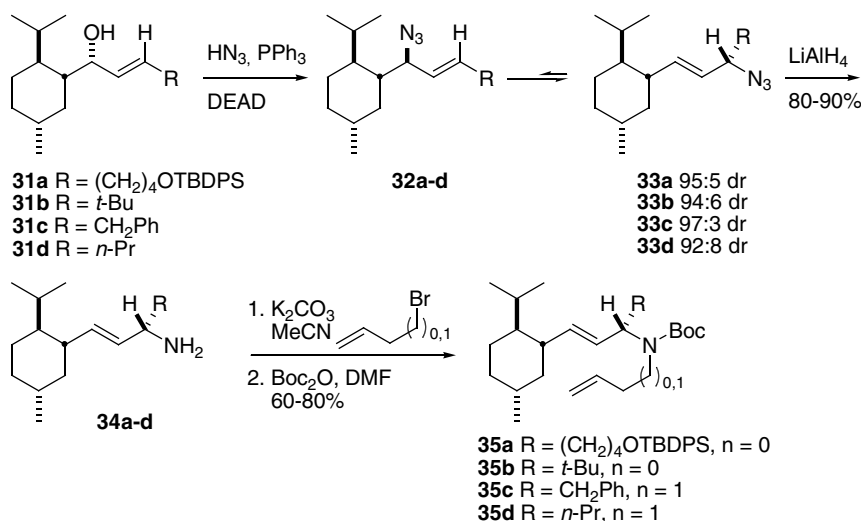
Scheme 5.

Encouraged by this initial success, we looked at the possibility of preparing the more biologically relevant *N*-heterocycles by this method. Two complementary and very useful transformations of alcohol **2** lead to the formation of chiral allylic amines bearing a tertiary or quaternary chiral carbon of high enantiomeric purity. The first uses a tandem Mitsunobu/azide rearrangement sequence on alcohols **31a–d** to make chiral allylic amines **34a–d** and is shown in Scheme 6 [13c]. The bulk of the menthyl fragment controls the thermodynamic ratio of the allylic azides **32** and **33**. Only regioisomers **33a–d** were observed by NMR, each with very good diastereomeric ratio. Reduction of the azide afforded the corresponding amines **34**, which were alkylated and protected as carbamates to give **35a–d**.

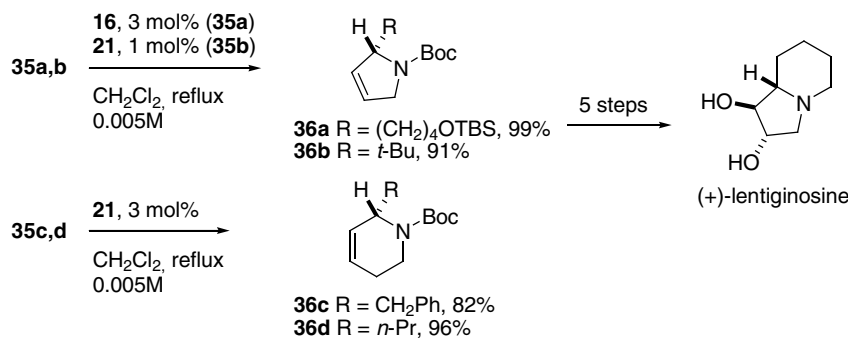
RCM cleavage of the auxiliary in the case of **35a–b** proceeded exceedingly well using catalyst **16** (3 mol%) or **21** (1 mol%) to give dihydropyrroles **36a** and **36b**, respectively (Scheme 7). Formation of tetrahydropyridines **36c–d** was nearly as efficient. As expected, protection of the amine function as a carbamate (Boc) had been necessary because the free secondary amines interfered with the RCM reac-

tion [21]. Reduction of the endocyclic alkene in **36d** gave (+)-*N*-Boc-conine [22] while **36a** was successfully transformed into the α -amyloglucosidase inhibitor (+)-lentiginosine in five steps [23]. Comparison of the optical rotations with literature data confirmed the enantiomeric purity of the products.

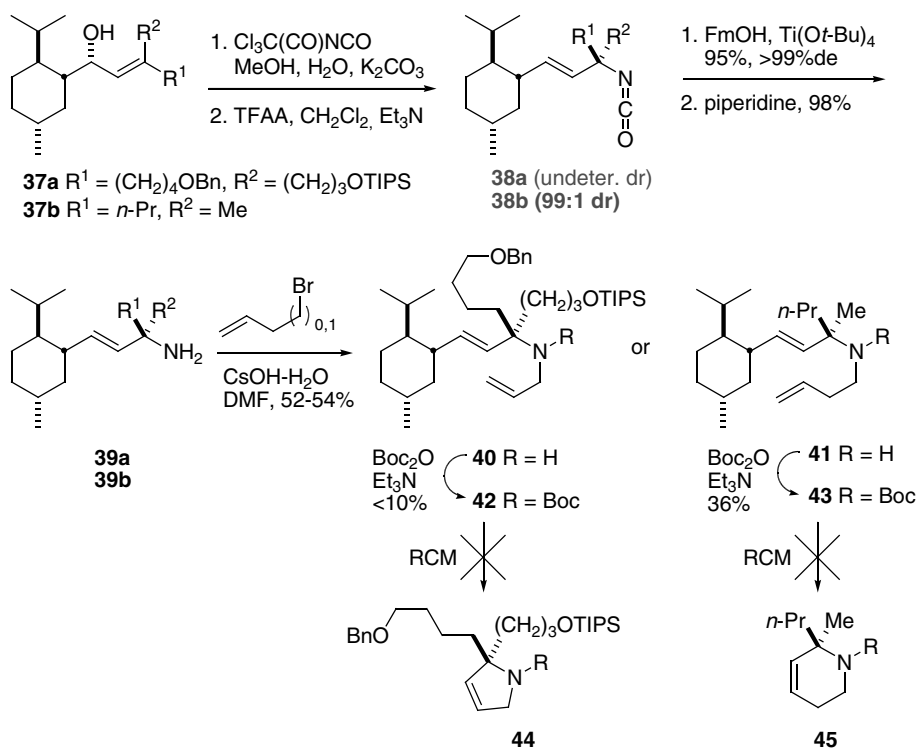
Primary amines **39a–b**, each bearing a quaternary chiral center next to nitrogen, were prepared in >98% de from alcohols **37a–b** by the stereospecific rearrangement of the corresponding cyanates to isocyanates **38a–b** as shown in Scheme 8 [24]. Amines **39a–b** were then alkylated with allylbromide or 1-butenylbromide to give **40** and **41**, respectively. Their protection proved exceedingly difficult. As it turns out, and annoyingly, it did not matter because allyl- or homoallylcarbamates **40**, **41**, **42**, or **43** refused to undergo the RCM reaction. Increasing the temperature and catalyst loading had little effect except to spur decomposition of the starting material. Once more, the difference in reactivity between carbamate **35d**, bearing a tertiary chiral carbon, and carbamate **43**, bearing a quaternary chiral carbon, appears out of proportion. These two compounds



Scheme 6.



Scheme 7.



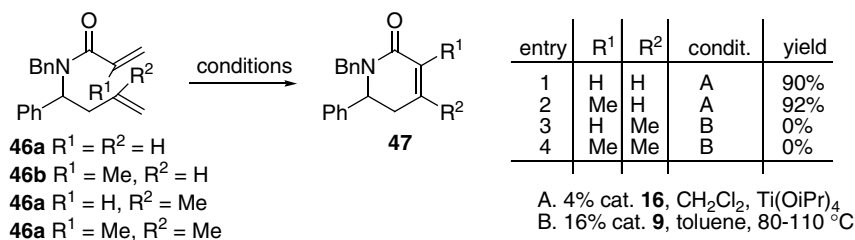
Scheme 8.

only differ by a methyl group. Clearly, steric effects are prominent in influencing the rate of cyclization, especially for the formation of six-membered rings. What was needed at this stage was a more reactive ruthenium alkylidene to increase the rate of cyclization.

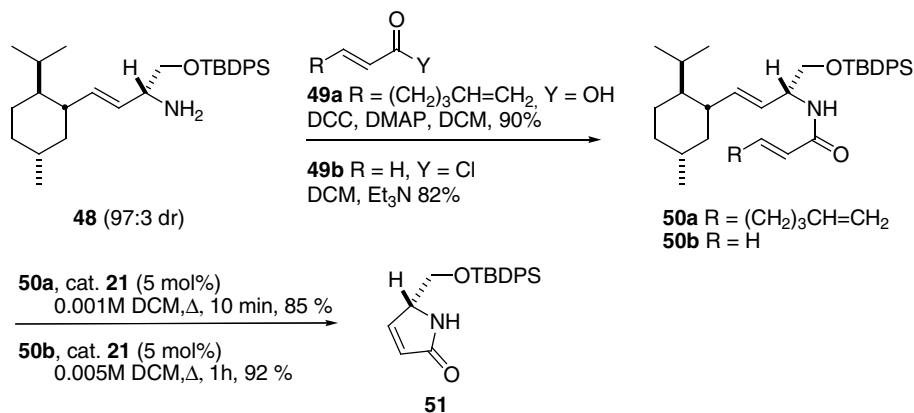
Enoic carbenes are thought to be much more reactive towards metathesis than normal ruthenium alkylidenes [25]. Nonetheless, this was an unnatural choice of functionality to initiate the RCM because α,β -unsaturated carbonyls are said to react sluggishly or not at all with the catalyst [26]. Grubbs and co-workers later reported that enoic carbenes are efficiently formed by the reaction of catalyst **9** with acrylates and reacted in cross metathesis with 1,1-disubstituted olefins [25b]. Interestingly, while a series of ester carbenes were found to be very unstable, the corresponding amide was indefinitely stable under the same conditions [27]. When considering a system like our own, we

must assume that initiation would occur at the conjugated alkene. Initiation at the internal double bond is certainly not in line with the results presented above. Tellingly, a report by Marco shows that the RCM reaction of unsaturated amides **46** using catalyst **9** fails unless initiation can take place at the non-conjugated alkene (Scheme 9, compare entries 2 vs. 3) [28].

For the reasons mentioned above, we initially used the relay metathesis concept [29] to effect the transformation of **50a** into **51**, believing that the reaction would benefit from an intramolecular relay for the formation of the amide ruthenium carbene (Scheme 10). However, it turns out to be unnecessary as the yield of lactam **51** was actually better when the acrylamide **50b** was used directly, though the reaction time was somewhat longer. The enantiomeric purity of the heterocycles were not determined and are assumed to be equal to the diastereomeric purity of the



Scheme 9.



Scheme 10.

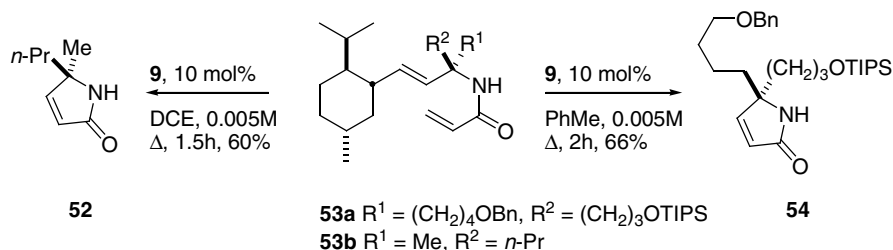
precursors. Racemization through Ru-catalyzed double bond migration is not possible here.

Encouraged by this result we tried the RCM cleavage of the auxiliary on amides **53a** and **53b** (made by the addition of vinylmagnesium bromide on isocyanate **38a** or **38b**, respectively) to effect formation of five-membered lactams bearing quaternary carbon centers. We were delighted to obtain decent yields of each of lactams **52** and **54** using 10 mol% **9** (Scheme 11).

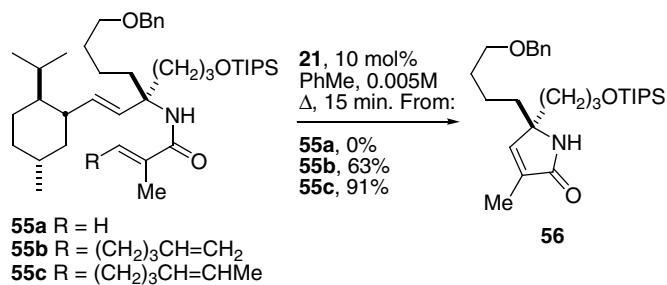
Could we perform the cleavage of the auxiliary to prepare a lactam bearing a quaternary carbon center and a trisubstituted double bond? We hoped so because our planned stereoselective syntheses of members of the daphniphyllane alkaloids [30] relies on the use of an intermediate very much like lactam **56**. Treatment of methacrylamide **55a** under the usual conditions gave only starting material (Scheme 12). However amide **55b** gave an encouraging 63% yield of the desired lactam **56**, the

remainder being methacrylamide **55a**. The latter compound is presumably formed from the intermolecular reaction of the amide carbene intermediate with the terminal double bond in starting amide **55b**. Thus, adding a methyl group on that terminal double bond sufficiently slowed this intermolecular reaction such that amide **55c** supplied the desired lactam **56** in 91% yield in only 15 min! A priori, we did not think RCM was possible on such a sterically loaded system and this example underscores the usefulness of RCM in synthesis.

The difference in reactivity between carbamate **43** and NH-amide **53b** (cf. Schemes 8 and 11) is intriguing. Our results with NH-amide **53a–b** are seemingly in contradiction with the failure to initiate an RCM from amide **46** reported by Marco and co-workers (cf. Scheme 9) [28]. In their case, however, the amide nitrogen was substituted with a benzyl group. Although the results presented herein do not represent a systematic study, we can suggest that the



Scheme 11.



Scheme 12.

amide helps the RCM cleavage of the auxiliary in two ways; firstly, the amide carbene intermediate is more reactive than normal ruthenium alkylidenes while it maybe easier to form than other enic carbenes [31,32]; secondly, the amide alleviates the need to further substitute the amine (with a Boc group for example) to prevent coordination of the free amine to the ruthenium [2b,21]. Consequently, the system is less congested and cyclizes faster.

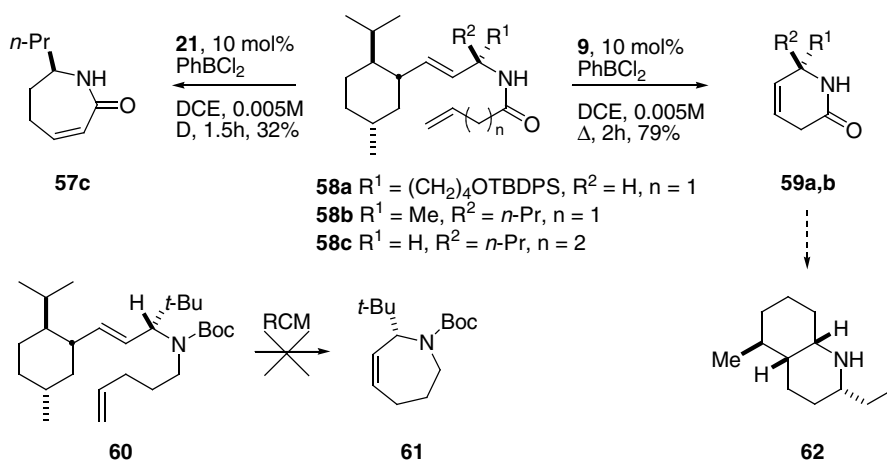
In support of the latter argument, six-membered lactams **58a,b** bearing a tertiary or quaternary stereocenter were efficiently prepared under similar conditions (Scheme 13, right). The use of a Lewis acid was necessary in this case because without it the alkylidene ruthenium species coordinates very efficiently to the amide carbonyl and the reaction stops after one catalytic turnover [33]. Compound **59a** is an advanced intermediate towards the synthesis of pumiliotoxin C **62** [34]. The formation of a seven-membered ring from **58c** was more difficult and led only to a 30% yield of lactam **57c** in which the alkene became conjugated with the amide carbonyl (Scheme 13, left). The remainder was a mixture of dimer and uncyclized products in which the double bond has migrated. Still, this result is better than previous ones starting from **60**, for which no cyclic product **61** was isolated. Thus the amide strategy will help in widening the scope of our methodology and we are hopeful we can improve on the formation of medium-size rings.

Chiral non-racemic *S*-heterocycles were also accessible using our methodology. We prepared *S*-thiocarbamates **64a–b** from the rearrangement of *O*-thiocarbamates derived from alcohols **63a–b**, as shown in Scheme 14 [35]. The cleavage of the *S*-thiocarbamates **64a–b** and concomitant alkylation of the resulting thiols was achieved with cesium carbonate in methanol. A portion of each sulfide **65a–c** was then oxidized with peracid to the corresponding sulfone **66a–c**.

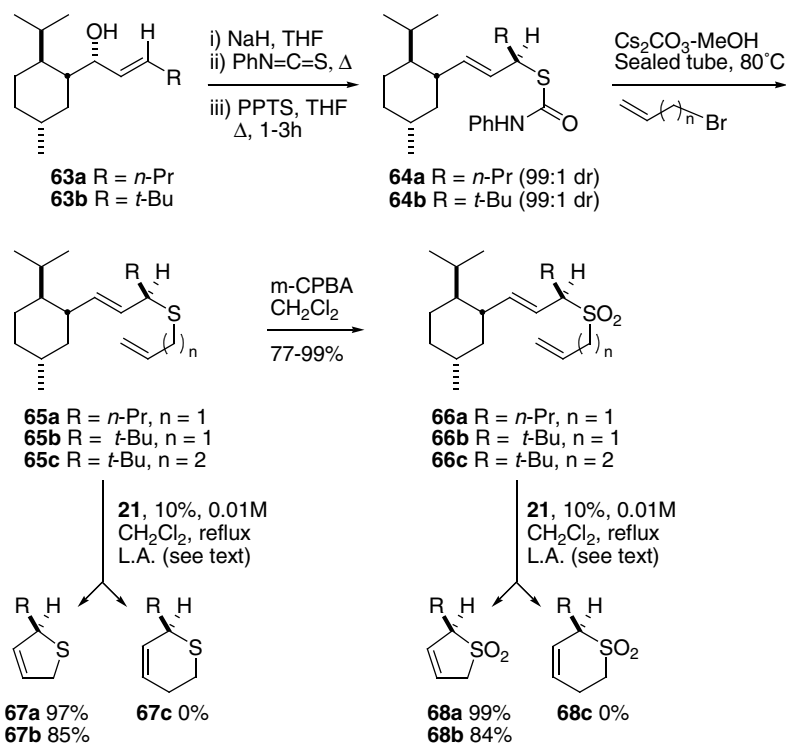
‘Unreliable’ would be a good word to describe the behaviour of those sulfides and sulfones in the RCM cleavage of the chiral auxiliary. Sulfide **65b** underwent the cyclization with high efficiency (85% yield) to give **67b** under mild conditions without the use of an external Lewis acid (Scheme 14). That in itself was a surprising result because sulfides are thought to be real poisons for ruthenium catalysts and the literature abounds in problematic RCM involving a sulfur atom [36]. A strong coordination between the sulfur and ruthenium metal center is often cited as the reason for this difficulty.

Surprisingly, the analogous homoallylic sulfide **65c** (R = *t*-Bu, *n* = 2) was inert to a huge series of experiments involving 10 different catalysts (Grubbs second generation type catalysts, Grela’s, Grubbs’ chlorophenylphosphines or bromopyridines, Hoveyda’s, Blechert’s, etc.) and dozens of reaction conditions! How could the sulfide in **65c** poison the catalysts when the sulfide in **65b** did not? Of course, we have seen such a drastic difference in rate of formation between five-membered and six-membered carbo- and *N*-heterocycles (vide supra) but only when they bore a quaternary carbon center. No such difference was seen on substrates having a tertiary center. Are the longer bonds between carbon and sulfur adding extra strain to the six-membered ring? It is true that very few dihydrothiopyranes have been prepared by RCM [36b,36f].

To add to the confusion, the *n*-propyl derivative **65a** would not undergo the RCM unless a Lewis acid was added to the reaction mixture. We have found that the best



Scheme 13.



Scheme 14.

additive was ((C₆H₆)RuCl₂)₂. This is, to our knowledge, the first time that a ruthenium additive has been used to improve a Ru-catalyzed RCM. The problem with **65a** is therefore a detrimental complexation between the sulfur and the metathesis catalyst. Only the added steric bulk of the *t*-butyl group in **65b** could have alleviated the need for a Lewis acid by hindering coordination between sulfur and ruthenium.

Sulfones **66a** and **66b** underwent the RCM reaction very efficiently and without additive in dichloromethane at 40 °C (99% and 84% yield, respectively). When the reaction was carried out in refluxing 1,2-dichloroethane, sulfur dioxide was extruded from the resulting sulfonolones **68a–b** and the corresponding dienes were recovered. No six-membered cyclic sulfone could be isolated when substrate **66c** was submitted to different catalysts and reaction conditions.

In summary, we have developed very useful synthetic sequences that terminate with a RCM cleavage of the chiral auxiliary and directly forms enantioenriched carbo- and heterocycles. The RCM reactions reported herein all involve a very sterically demanding 1,2-disubstituted double bond. One of the salient features of these RCM reactions is that the propagating ruthenium alkylidene is unusually bulky, which slows undesired reaction rates to the advantage of productive ones. The difference in cyclization rates of some five vs. six-membered rings were sometimes stunning. Many of the chiral heterocycles formed by RCM were or are currently being used to prepare natural products.

3. Experimental section

3.1. Syntheses of alcohols **31a**, **37a–b**: general procedure

The vinyl iodide (1.2 eq) was dissolved in anhydrous diethyl ether and the solution was cooled to –78 °C. A 2.5 M solution of *n*-BuLi in hexanes (1.2 eq) was added at –78 °C dropwise. The reaction was stirred at –78 °C during 30 min, warmed to rt and stirred for 30 min at rt. A 2 M solution of AlMe₃ in hexanes (2.5 eq) was added at rt. After cooling to –78 °C, menthyl 3-carboxaldehyde (1 eq) was added and the reaction was stirred overnight while allowing to slowly warm to rt. The reaction mixture was quenched with saturated K₂CO₃ and then 2 N HCl was added to dissolve carbonate salts. The phases were separated and the aqueous phase was extracted three times with Et₂O. The organic layers were combined, washed once with brine, dried over magnesium sulfate and concentrated under reduced pressure to give a yellow oil. Diastereomeric excess (% de) were evaluated by GC or HPLC. The crude product was purified by flash chromatography on a silica gel column eluting with hexanes and ethyl acetate.

3.1.1. Alcohol **31a**

Colorless oil (9.41 g, 56%, >99% de by HPLC). ¹H NMR (CDCl₃, 300 MHz): δ 7.66 (dd, 4H, *J* = 7.7 Hz, 1.7 Hz), 7.45–7.34 (m, 6H), 5.65–5.47 (m, 2H), 4.36 (d, 1H, *J* = 4.4 Hz), 3.66 (t, 2H, *J* = 6.1 Hz), 2.13 (qd, 1H, *J* = 6.6 Hz, 2.2 Hz), 2.04 (q, 2H, *J* = 7.2 Hz), 1.72–1.46 (m, 9H), 1.44–1.24 (m, 3H), 1.04 (s, 9H), 1.05–0.79 (m,

3H), 0.93 (d, 3H, $J = 7.2$ Hz), 0.87 (d, 3H, $J = 6.6$ Hz), 0.76 (d, 3H, $J = 7.2$ Hz). IR (neat, cm^{-1}): 3447, 3069, 2956, 2931, 2859, 1472, 1428, 1111, 973. LRMS (m/z (relative intensity)): 449 ($(\text{M}-\text{C}_4\text{H}_9)^+$, 10), 293 (14), 233 (21), 199 (100), 177 (22), 137 (49), 109 (29), 95 (64), 81 (39). HRMS calc. for $\text{C}_{29}\text{H}_{41}\text{O}_2\text{Si}$: 449.2876, found 449.2870. $[\alpha]_{\text{D}}^{20} = -7.7^\circ$ (c 2.57, CHCl_3).

3.1.2. Alcohol 37a

Colorless oil (636 mg, 97%, >99% de by GC). ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.35–7.27 (m, 5H), 5.38 (d, 1H, 8.1 Hz), 4.68 (d, 1H, $J = 8.1$ Hz), 4.51 (s, 2H), 3.66 (t, 2H, $J = 6.3$ Hz), 3.48 (t, 2H, $J = 6.3$ Hz), 2.24–2.14 (m, 2H), 2.12–2.01 (m, 3H), 1.74–1.46 (m, 9H), 1.36–1.22 (m, 4H), 1.15–1.00 (m, 5H), 1.06 (d, 18H, $J = 2.8$ Hz), 0.96–0.63 (m, 3H), 0.93 (d, 3H, $J = 6.6$ Hz), 0.89 (d, 3H, $J = 6.6$ Hz), 0.77 (d, 3H, $J = 7.2$ Hz). IR (neat) ν (cm^{-1}) 3573–3294 (br), 3029, 2945, 2865, 1461, 1099, 876. LRMS (m/z , relative intensity) 555 ($[\text{M}-\text{OH}]^+$, 1), 529 ($(\text{M}-\text{C}_3\text{H}_7)^+$, 20), 433 (50), 259 (50), 151 (43), 91 (100), 83 (60). HRMS calc. for $\text{C}_{27}\text{H}_{42}\text{O}_2$ ($[\text{M}-\text{C}_3\text{H}_7]^+$): 529.4077, found: 529.4064. $[\alpha]_{\text{D}}^{20} = -18.2^\circ$ ($c = 1.52$, CHCl_3).

3.1.3. Alcohol 37b

White solid (464 mg, 77%, 99% de by GC); m.p.: 30–31 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 5.34 (d, 1H, $J = 8.2$ Hz), 4.67 (dd, 1H, $J = 8.3$ Hz, 3.9 Hz), 2.19 (septd, 1H, $J = 6.6$ Hz, 1.7 Hz), 1.98 (t, 2H, $J = 7.7$ Hz), 1.73–1.65 (m, 3H), 1.63 (s, 3H), 1.44 (sext, 2H, $J = 7.5$ Hz), 1.38–1.28 (m, 3H), 1.12 (d, 1H, $J = 4.4$ Hz), 0.95–0.86 (m, 12H), 0.79 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (75.5 MHz, CDCl_3) δ 136.7 (s), 126.9 (d), 67.6 (d), 44.8 (d), 43.1 (t), 41.8 (d), 35.1 (t), 34.0 (t), 32.7 (d), 26.3 (d), 24.2 (t), 22.8 (q), 21.6 (q), 20.8 (q), 16.4 (t), 15.5 (q), 13.7 (q). IR ($\text{CHCl}_3/\text{NaCl}$) ν (cm^{-1}) 3349 (br), 2955, 2925, 2871, 1450. MSLR (m/z , relative intensity) 252 (M^+ , 22), 209 ($(\text{M}^+-\text{C}_3\text{H}_7)$, 10), 113 (100). MSHR calc. for $\text{C}_{17}\text{H}_{32}\text{O}$: 252.2453, found: 252.2448. $[\alpha]_{\text{D}}^{20} = -51.1$ ($c = 1.15$, CHCl_3).

3.2. Synthesis of azide 33a

In a 50 mL rb flask, was dissolved the allylic alcohol **31a** (1.50 g, 2.96 mmol) and triphenylphosphine (1.55 g, 5.92 mmol) in benzene (30 mL) and this solution was cooled to 0 $^\circ\text{C}$. A solution of hydrazoic acid (4.2 mL, 1.4 M in benzene, 5.92 mmol) and diethylazodicarboxylate (DEAD) (1.03 g, 5.92 mmol) were added dropwise simultaneously at 0 $^\circ\text{C}$ and the reaction mixture was stirred for 6 h letting the temperature warm slowly to rt. The resulting reaction mixture was then diluted with hexanes and filtered over a pad of celite to remove the triphenylphosphine oxide. The mother liquor was washed with two portions of 70:30 MeOH/ H_2O , once with brine, dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure to give a yellow oil. The crude product was purified on silica gel with 5:95/EtOAc:hexanes as eluant to afford a colorless oil (1.55 g, 98%, 97% de by HPLC). ^1H

NMR (CDCl_3 , 300 MHz): δ 7.66 (dd, 4H, $J = 7.7$ Hz, 1.7 Hz), 7.45–7.34 (m, 6H), 5.51–5.43 (m, 1H), 5.36–5.27 (m, 1H), 3.76 (q, 1H, $J = 6.6$ Hz), 3.64 (t, 2H, $J = 6.6$ Hz), 1.96–1.85 (m, 2H), 1.75–1.70 (m, 1H), 1.65–1.25 (m, 10H), 1.04 (s, 9H), 1.05–0.83 (m, 3H), 0.86 (d, 3H, $J = 7.1$ Hz), 0.85 (d, 3H, $J = 6.6$ Hz), 0.71 (d, 3H, $J = 6.6$ Hz). IR (neat, cm^{-1}): 3072, 3049, 2962, 2868, 2095, 1471, 1428, 1237, 1111, 973. LRMS (m/z (relative intensity)): 503 ($(\text{M}-\text{N}_2)^+$, 8), 446 (100), 308 (11), 248 (30), 199 (68), 183 (23), 135 (20), 81 (18). HRMS calc. for $\text{C}_{33}\text{H}_{53}\text{N}_4\text{OSi}$: 549.3988, found 549.3984 (for $(\text{MNH}_4)^+$). $[\alpha]_{\text{D}}^{20} = -25.1$ (c 3.67, CHCl_3).

3.3. Synthesis of amine 34a

In a 100 mL rb flask was dissolved the azide **33a** (1.00 g, 1.88 mmol) in THF (20 mL). This solution was cooled to 0 $^\circ\text{C}$ and LiAlH_4 (powder 95%, 107 mg, 2.82 mmol) was added by small portions. The resulting mixture in stirred at 0 $^\circ\text{C}$ for 10 min and then at rt. After 18 h, the reaction mixture was cooled to 0 $^\circ\text{C}$ and treated with water and a 1 N aqueous solution of HCl. The suspension was then filtered on a pad of celite and the filtrate was treated with a 1 N aqueous solution of NaOH. The aqueous phase was extracted with three portions of EtOAc and the combined organic extracts were washed once with water and once with brine, dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure to give a colorless oil. The crude product was purified on silica gel with 30:70/EtOAc:hexanes as eluant to afford a colorless oil (820 mg, 86%). ^1H NMR (CDCl_3 , 300 MHz): δ 7.66 (dd, 4H, $J = 7.7$, 1.7 Hz), 7.45–7.34 (m, 6H), 5.31–5.28 (m, 2H), 3.64 (t, 2H, $J = 6.6$ Hz), 3.24 (m, 1H), 1.85 (qi, 2H, $J = 6.6$ Hz), 1.73–1.67 (m, 1H), 1.62–1.52 (m, 5H), 1.49–1.26 (m, 5H), 1.04 (s, 9H), 1.01–0.74 (m, 3H), 0.85 (d, 3H, $J = 6.6$ Hz), 0.84 (d, 3H, $J = 6.6$ Hz), 0.69 (d, 3H, $J = 6.6$ Hz). IR (neat, cm^{-1}): 3891, 3366, 3070, 2955, 2929, 2859, 1472, 1428, 1111, 971. LRMS (m/z (relative intensity)): 506 ($(\text{MH})^+$, 84), 489 (49), 448 (100), 293 (30), 194 (100), 137 (13), 95 (8). HRMS calc. for $\text{C}_{33}\text{H}_{52}\text{NOSi}$: 506.3818, found 506.3821. $[\alpha]_{\text{D}}^{20} = -20.5^\circ$ (c 2.34, CHCl_3).

3.4. Synthesis of carbamate 35a

In a 100 mL r.b. flask was dissolved the amine **34a** (1.58 g, 3.114 mmol) in acetonitrile (31 mL). Anhydrous K_2CO_3 (452 mg, 3.270 mmol) was added into the solution and this solution was stirred 5 min at rt. Then, the allyl bromide (414 mg, 3.425 mmol) was added very slowly (20 $\mu\text{L}/\text{min}$) and the resulting suspension was stirred at rt for 1.5 h and an excess of allyl bromide (0.2 eq) was added. The resulting mixture was stirred again for a another 2 h at rt, diluted in water and extracted with three portions of EtOAc. The combined organic extracts were washed once with brine, dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure to give a yellow oil. The crude product was purified on silica gel with 1:1/Et₂O:hex-

anes as eluant to afford a colorless oil (986 mg, 59%). ^1H NMR (300 MHz, CDCl_3): δ 7.65 (dd, 4H, $J = 7.7$, 1.7 Hz), 7.44–7.34 (m, 6H), 5.91 (ddt, 1H, $J = 17.0$, 16.5, 6.1 Hz), 5.27 (dd, 1H, $J = 15.4$, 8.8 Hz), 5.17–5.07 (m, 3H), 3.63 (t, 2H, $J = 6.6$ Hz), 3.28 (dd, 1H, $J = 13.8$, 5.5 Hz), 3.10 (dd, 1H, $J = 13.8$, 6.6 Hz), 3.02–2.90 (m, 1H), 1.98–1.83 (m, 2H), 1.74–1.67 (m, 1H), 1.59–1.24 (m, 10H), 1.04 (s, 9H), 1.02–0.64 (m, 3H), 0.87 (d, 6H, $J = 6.6$ Hz), 0.83 (d, 3H, $J = 6.6$ Hz), 0.70 (d, 3H, $J = 6.6$ Hz). IR (film) ν (cm^{-1}): 3071, 2945, 2930, 2859, 1471, 1455, 1427, 1111, 909. LRMS (m/z , relative intensity): 545 ((M^+) , 2), 504 ($(\text{M}-\text{C}_3\text{H}_5)^+$, 23), 488 ($(\text{M}-\text{C}_4\text{H}_9)^+$, 31), 234 (100), 199 (18), 183 (10), 96 (43). HRMS calc. for $\text{C}_{36}\text{H}_{55}\text{NOSi}$: 545.4053, found 545.4038. $[\alpha]_{\text{D}}^{20} = -21.7$ ($c = 1.09$, CHCl_3).

In a 100 mL rb flask was dissolved the alkylated amine (1.31 g, 2.400 mmol) in DMF (20 mL) and this solution was stirred at rt for 5 min. Then, triethylamine (368 mg, 3.600 mmol) was added and this solution was stirred for another 5 min at rt and the di-*tert*-butyldicarbonate (786 mg, 3.600 mmol) was added and this resulting mixture was stirred at rt during 23 h. The mixture was then treated with a saturated solution of NH_4Cl and the aqueous phase was extracted with three portions of EtOAc and the combined organic extracts were washed once with water and once with brine, dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure to give a yellow oil. The crude product was purified on silica gel with 3:97/AcOEt:hexanes as eluant to afford a colorless oil (1.26 g, 82%). ^1H NMR (CDCl_3 , 300 MHz): δ 7.65 (dd, 4H, $J = 7.7$, 1.7 Hz), 7.44–7.34 (m, 6H), 5.82–5.70 (m, 1H), 5.40–5.23 (m, 2H), 5.10 (d, 1H, $J = 17.2$ Hz), 5.02 (d, 1H, $J = 7.9$ Hz), 3.63 (t, 2H, $J = 6.6$ Hz), 1.90–1.51 (m, 9H), 1.44 (s, 9H), 1.35–1.25 (m, 6H), 1.04 (s, 9H), 0.97–0.79 (m, 10 H), 0.67 (d, 3H, $J = 6.6$ Hz). LRMS (m/z (relative intensity)): 589 ($(\text{M}-\text{C}_4\text{H}_9)^+$, 1), 532 (44), 455 (61), 282 (51), 278 (100), 235 (70), 199 (41), 140 (49). HRMS calc. for $\text{C}_{37}\text{H}_{55}\text{NO}_3\text{Si}$: 589.3951, found 589.3942.

3.5. Synthesis of dihydropyrrole **36a**

In a 500 mL rb flask was dissolved the carbamate **35a** (1.00 g, 1.548 mmol) in dry CH_2Cl_2 (310 mL, 0.005 M) and the reaction was refluxed for 10 min. The reflux was stopped and catalyst **16** (63.7 mg, 0.0774 mmol) was added in small portions and the reaction mixture was refluxed for 18 h. The resulting solution was concentrated under reduced pressure and the crude product was purified on silica gel with 1:20/EtOAc:hexanes as eluant to afford a colorless oil (743 mg, 100%). ^1H NMR (300 MHz, CDCl_3): δ 7.65 (dd, 4H, $J = 7.7$, 2.2 Hz), 7.44–7.33 (m, 6H), 5.75–5.68 (br d, 2H, $J = 6.6$ Hz), 4.50 (m, 1H), 4.17 (br d, 1H, $J = 13.2$ Hz), 3.98 (dd, 1H, $J = 9.9$, 5.5 Hz), 3.63 (t, 2H, $J = 6.6$ Hz), 1.69–1.51 (m, 4H), 1.46 (s, 9H), 1.35–1.24 (m, 2H), 1.04 (s, 9H). IR (neat) ν (cm^{-1}): 3071, 2924, 2861, 1704, 1697, 1427, 1392, 1174, 1111, 910. LRMS (m/z , relative intensity): 480 ($(\text{MH})^+$, 39), 380 (62), 366

(58), 288 (49), 83 (100). HRMS calc. for $\text{C}_{29}\text{H}_{42}\text{NO}_3\text{Si}$ ($\text{MH})^+$: 480.2934, found: 480.2942. $[\alpha]_{\text{D}}^{20} = +3.5$ ($c = 1.25$, CHCl_3).

3.6. Syntheses of isocyanates **38a–b**: general procedure

Trichloroacetylisocyanate (1.5 eq) was added dropwise to a solution of the alcohol (1 eq) in CH_2Cl_2 at 0 °C. The solution was stirred for 1 h at 0 °C. The solvent was then evaporated under reduced pressure and the resulting precipitate was dissolved in a 2:1 mixture of methanol and water. This solution was cooled to 0 °C and potassium carbonate (3 eq) was slowly added. The mixture was allowed to warm slowly to room temperature while stirring overnight. Methanol was then evaporated under reduced pressure and the aqueous layer was extracted with 3×15 mL of dichloromethane. The organic layers were combined, washed with brine, dried with MgSO_4 , filtered and evaporated. The crude compound can be used directly in the next step or it can be purified by flash chromatography eluting with EtOAc/hexanes.

Triethylamine (3 eq) and TFAA (0.95 eq) were both added dropwise to a solution of the allylcarbamate (1 eq) in CH_2Cl_2 at 0 °C. The solution was stirred for 15 min at 0 °C before quenching with saturated aqueous NH_4Cl (15 mL). The layers were separated and the aqueous layer was extracted with 3×15 mL of dichloromethane. The organic layers were combined, washed with brine, dried with MgSO_4 , filtered and evaporated. The crude compound was purified by flash chromatography eluting with Et_2O /hexanes (5:95).

3.6.1. Isocyanate **38a**

Colorless oil (1.07 g, 99%). ^1H NMR (300 MHz, CDCl_3) δ 7.38–7.25 (m, 5H), 5.42 (dd, 1H, $J = 15.3$, 9.6 Hz), 5.17 (d, 1H, $J = 15.3$ Hz), 4.50 (s, 2H), 3.73–3.63 (m, 2H), 3.46 (t, 2H, $J = 6.3$ Hz), 1.96–1.17 (m, 15H), 1.16–0.99 (m, 23H), 0.95–0.82 (m, 3H), 0.86 (d, 6H, $J = 6.6$ Hz), 0.68 (d, 3H, $J = 7.1$ Hz). IR (neat) ν (cm^{-1}) 3044, 2946, 2866, 2263, 1457, 1105. LRMS (m/z , relative intensity) 554 ($[\text{M}-\text{C}_3\text{H}_7]^+$, 22), 421 (12), 91 (100). HRMS calc. for $\text{C}_{34}\text{H}_{56}\text{NO}_3\text{Si}$ ($[\text{M}-\text{C}_3\text{H}_7]$): 554.4029, found: 554.4041. $[\alpha]_{\text{D}}^{20} = -31.6$ ($c = 1.29$, CHCl_3).

3.6.2. Isocyanate **38b**

Colorless oil (43 mg, 95%, >99% de by GC). ^1H NMR (300 MHz, CDCl_3) δ 5.42 (dd, 1H, $J_1 = 15.4$ Hz, $J_2 = 8.8$ Hz), 5.31 (d, 1H, $J = 15.4$ Hz), 1.93–1.70 (m, 3H), 1.64–1.52 (m, 4H), 1.49–1.26 (m, 4H), 1.36 (s, 3H), 1.02–0.81 (m, 6H), 0.92 (d, 3H, $J = 7.2$ Hz), 0.87 (d, 3H, $J = 6.6$ Hz), 0.69 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (75.5 MHz, CDCl_3) δ 133.6 (d), 133.1 (d), 110.0 (s), 61.6 (s), 47.1 (d), 45.7 (t), 44.2 (d), 43.2 (t), 35.1 (t), 32.4 (d), 29.4 (q), 28.1 (d), 24.1 (t), 22.5 (q), 21.3 (q), 17.6 (t), 15.3 (q), 14.1 (q). IR (neat/ NaCl) ν (cm^{-1}) 2957, 2929, 2873, 2260, 1455, 972. MSLR (m/z , relative intensity) 277 (M^+ , 5), 234 (M^+-HNCO , 58), 191 (38), 96 (100). MSHR calc.

for $C_{18}H_{31}NO$: 277.2405, found: 277.2399. $[\alpha]_D^{20} = -73.4$ ($c = 1.23$, $CHCl_3$).

3.7. Syntheses of amines **39a–b**: general procedure

$Ti(Ot-Bu)_4$ (0.1 or 0.2 eq) was added to a solution of the isocyanate (1 eq) and 9-fluorene-methanol (1.5 eq) in benzene (10 ml) at 0 °C. The solution was refluxed for 3 h before quenching with saturated aqueous NH_4Cl (20 ml). The layers were separated and the aqueous layer was extracted with 3×20 mL of Et_2O . The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and evaporated.

Piperidine (3 eq) was added to a solution of the Fmoc-protected amine (1 eq) in a 2:1 mixture of DMF and CH_2Cl_2 . The solution was stirred at rt overnight before quenching with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with 3×20 mL of Et_2O . The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and evaporated. The crude compound was purified by flash chromatography eluting with $EtOAc$ /hexanes/ Et_3N (25:74:1).

3.7.1. Amine **39a**

Colorless oil (506 mg, 98%). 1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.39–7.25 (m, 5H), 5.36–5.18 (m, 2H), 4.49 (s, 2H), 3.65 (t, 2H, $J = 5.5$ Hz), 3.48–3.42 (m, 2H), 1.97–1.21 (m, 18H), 1.11–0.94 (m, 23H), 0.91–0.78 (m, 2H), 0.85 (d, 3H, $J = 6.6$ Hz), 0.84 (d, 3H, $J = 7.2$ Hz), 0.68 (d, 3H, $J = 7.1$ Hz). IR (neat) ν (cm^{-1}) 3032, 2944, 2865, 1457, 1104. LRMS (m/z , relative intensity) 571 (M^+ , 2), 528 ($[M-C_3H_7]^+$, 10), 409 (100), 356 (65), 91 (68). HRMS calc. for $C_{36}H_{65}NO_2Si$: 571.4784, found: 571.4773. $[\alpha]_D^{20} = -22.4$ ($c = 1.21$, $CHCl_3$).

3.7.2. Amine **39b**

Colorless oil (308 mg, 92%). 1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.42 (d, 1H, $J = 16.0$ Hz), 5.21 (dd, 1H, $J = 16.0$, 9.1 Hz), 1.91–1.84 (m, 2H), 1.82–1.69 (m, 1H), 1.63–1.54 (m, 2H), 1.40–1.19 (m, 6H), 1.13 (s, 3H), 1.02–0.78 (m, 6H), 0.91 (d, 3H, $J = 7.2$ Hz), 0.86 (d, 3H, $J = 6.6$ Hz), 0.69 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 138.2 (d), 131.2 (d), 52.7 (s), 47.2 (d), 46.3 (t), 44.5 (d), 43.5 (t), 35.1 (t), 32.4 (d), 28.8 (q), 27.9 (d), 24.0 (t), 22.5 (q), 21.3 (q), 17.4 (t), 15.1 (q), 14.6 (q). IR (neat, cm^{-1}) 2955, 2928, 2916, 2871, 1455, 975. LRMS (m/z , relative intensity) 250 ($(M-H)^+$, 1), 236 ($(M-CH_3)^+$, 16), 234 ($(M-NH_3)^+$, 3), 208 ($(M-C_3H_7)^+$, 100). HRMS calc. for $C_{17}H_{32}N$ ($M-H$): 250.2535, found: 250.2540. $[\alpha]_D^{20} = -65.3$ ($c = 1.03$, $CHCl_3$).

3.8. Synthesis of amine **40**

A mixture of the amine **39a** (161 mg, 0.28 mmol), $CsO \cdot H_2O$ (45 mg, 0.27 mmol), and 4 Å MS (75 mg) were stirred in DMF (0.5 ml) for 30 min before adding allyl

bromide (30 μ l, 0.35 mmol). The resulting suspension was stirred at room temperature for 48 h before quenching with saturated aqueous $NaHCO_3$ (10 ml). The layers were separated and the aqueous layer was extracted with 3×10 mL of Et_2O . The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and evaporated. The crude compound was purified by flash chromatography eluting with Et_2O /hexanes (20:80) to yield 93 mg (54%) of the desired compound as a colorless oil. 1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.37–7.25 (m, 5H), 5.92 (ddt, 1H, $J = 16.8$, 10.8, 5.8 Hz), 5.26–5.15 (m, 2H), 5.14 (dd, 1H, $J = 16.8$, 1.1 Hz), 5.03 (d, 1H, $J = 10.8$ Hz), 4.49 (s, 2H), 3.67–3.64 (m, 2H), 3.45 (t, 2H, $J = 6.8$ Hz), 3.03 (d, 2H, $J = 5.8$ Hz), 1.95–1.15 (m, 18H), 1.14–0.91 (m, 22H), 0.90–0.79 (m, 2H), 0.85 (d, 6H, $J = 7.2$ Hz), 0.67 (d, 3H, $J = 6.6$ Hz). IR (neat) ν (cm^{-1}) 3065, 3032, 2943, 2865, 1464, 1103. LRMS (m/z , relative intensity) 611 (M^+ , 2), 448 (100), 396 (97). HRMS calc. for $C_{39}H_{69}NO_2Si$: 611.5097, found: 611.5078. $[\alpha]_D^{20} = -27.2$ ($c = 0.37$, $CHCl_3$).

3.8.1. Amine **41**

Same procedure as per amine **40**. 1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.75 (ddt, 1H, $J = 17.0$, 9.9, 7.2 Hz), 5.23 (d, 1H, $J = 16.0$ Hz), 5.17–5.00 (m, 4H), 2.51 (t, 2H, $J = 7.2$ Hz), 2.20 (q, 2H, $J = 7.2$ Hz), 1.93–1.78 (m, 2H), 1.74–1.70 (m, 1H), 1.63–1.53 (m, 2H), 1.46–1.29 (m, 3H), 1.28–1.16 (m, 2H), 1.08 (s, 3H), 1.02–0.79 (m, 7H), 0.90 (d, 3H, $J = 7.7$ Hz), 0.86 (d, 3H, $J = 6.6$ Hz), 0.69 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 136.8 (d), 136.1 (d), 133.8 (d), 116.1 (t), 56.2 (s), 47.2 (d), 45.0 (d), 43.7 (t), 43.6 (t), 41.3 (t), 35.2 (t), 34.9 (t), 32.5 (d), 28.1 (d), 24.0 (t), 23.6 (q), 22.6 (q), 21.4 (q), 17.1 (t), 15.1 (q), 14.7 (q). IR (neat, cm^{-1}) 3077, 2956, 2928, 2871, 2843, 1695, 1641, 1455, 1370, 978, 912. LRMS (m/z , relative intensity) 304 ($(M-H)^+$, 1), 290 ($(M-CH_3)^+$, 7), 262 ($(M-C_3H_7)^+$, 100), 84 (50). HRMS calc. for $C_{21}H_{38}N$ ($M-H$): 304.3004, found: 304.3009. $[\alpha]_D^{20} = -67.0$ ($c = 1.00$, $CHCl_3$).

3.9. Synthesis of carbamate **43**

The amine **41** (126 mg, 0.41 mmol) and triethylamine (86 μ l, 0.62 mmol) were dissolved in dimethylformamide (4 mL). Then, $(Boc)_2O$ (135 mg, 0.62 mmol) was added to the reaction mixture. The reaction was stirred at rt for a week. A saturated solution of $NaHCO_3$ was poured in the reaction mixture and the product was extracted with 3×10 mL of diethyl ether. Organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting light yellow oil was purified by flash chromatography (from 100% hexanes to 70% diethyl ether in hexanes) to yield pure (*R*)-protected amine (60 mg, 36%) as a colorless oil and 40 mg of starting material (32%). 1H NMR (300 MHz, $CDCl_3$) δ 5.71 (ddt, 1H, $J = 17.0$, 9.9, 6.6 Hz), 5.62 (d, 1H, $J = 15.9$ Hz), 5.25 (dd, 1H, $J = 15.9$, 9.4 Hz), 5.02 (dd, 1H, $J = 17.0$, 1.7 Hz), 4.99 (dd, 1H, $J = 9.9$, 1.7 Hz), 3.22 (t, 2H,

$J = 8.0$ Hz), 2.22 (sept, 1H, $J = 7.4$ Hz), 1.92–1.70 (m, 6H), 1.66–1.54 (m, 2H), 1.45 (s, 9H), 1.40 (s, 3H), 1.22 (sext., 2H, $J = 7.7$ Hz), 1.03–0.78 (m, 8H), 0.87 (d, 3H, $J = 7.2$ Hz), 0.86 (d, 3H, $J = 6.6$ Hz), 0.70 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (75.5 MHz, CDCl_3) δ 155.4 (s), 135.8 (d), 134.6 (d), 132.8 (d), 115.8 (t), 78.9 (s), 61.4 (s), 47.3 (d), 45.7 (t), 44.9 (d), 43.2 (t), 42.3 (t), 35.3 (t), 35.1 (t), 32.4 (d), 28.5 (q), 28.2 (d), 24.4 (q), 24.1 (t), 22.5 (q), 21.4 (q), 17.6 (t), 15.3 (q), 14.5 (q). IR ($\text{CHCl}_3/\text{NaCl}$) ν (cm^{-1}) 3077, 2956, 2929, 2871, 1699, 1455, 1385, 1365, 1173, 1134. LRMS (m/z , relative intensity) 405 (M^+ , 1), 349 ($(\text{M}-\text{C}_4\text{H}_8)^+$, 88), 306 (100), 262 (47), 235 (61), 168 (50), 97 (77). HRMS calc. for $\text{C}_{26}\text{H}_{47}\text{NO}_2$: 405.3607, found: 405.3604. $[\alpha]_{\text{D}}^{20} = -37.8$ ($c = 1.02$, CHCl_3).

3.9.1. Amine 48

Same procedure as per amine **34a**. Colorless oil (34 mg, 73%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.66 (d, 4H, $J = 7.7$ Hz), 7.46–7.34 (m, 6H), 5.45–5.40 (m, 2H), 3.73–3.61 (m, 1H), 3.60–3.50 (m, 2H), 2.45–1.82 (m, 2H), 1.81–1.64 (m, 2H), 1.63–1.56 (m, 2H), 1.38–1.21 (m, 1H), 1.25 (s, 2H), 1.06 (s, 9H), 0.97–0.75 (m, 3H), 0.84 (d, 3H, $J = 6.1$ Hz), 0.81 (d, 3H, $J = 7.1$ Hz), 0.64 (d, 3H, $J = 6.6$ Hz). IR (neat, cm^{-1}): 2953, 2927, 2862, 1111, 703. LRMS (m/z (relative intensity)): 406 ($\text{M}^+-\text{C}_4\text{H}_9$, 30), 194 (100). HRMS calc. for $\text{C}_{26}\text{H}_{36}\text{NOSi}$ ($\text{M}^++\text{C}_4\text{H}_9$): 406.2566, found: 406.2570. $[\alpha]_{\text{D}}^{20} = -27.7$ ($c = 1.06$, CHCl_3).

3.10. Synthesis of amide 50a

Amine **48** (823 mg, 1.79 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. DCC (736 mg, 3.57 mmol) and DMAP (43.7 mg, 0.358 mmol) were added and the mixture was stirred 1 h at 0 °C. The reaction mixture was quenched with a saturated solution of ammonium chloride. Phases were separated and the aqueous phase was extracted twice with pentane. Organic phases were combined, washed once with brine, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. Flash chromatography on silica gel, eluting with hexanes and ethyl acetate (9:1) furnished a clear oil (940 mg, 90%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.63 (d, 4H, $J = 7.7$ Hz), 7.43–7.34 (m, 6H), 6.79 (dt, 1H, $J = 14.8$, 7.2 Hz), 5.80 (ddt, 1H, $J = 17.0$, 10.4, 6.8 Hz), 5.73–5.62 (m, 2H), 5.49 (dd, 1H, $J = 15.4$, 4.4 Hz), 5.41 (dd, 1H, $J = 15.4$, 7.1 Hz), 5.05–4.96 (m, 2H), 4.68–4.56 (m, 1H), 3.74 (d, 2H, $J = 3.8$ Hz), 2.19 (q, 2H, $J = 7.2$ Hz), 2.09 (q, 2H, $J = 6.8$ Hz), 1.96–1.73 (m, 2H), 1.72–1.47 (m, 4H), 1.42–1.15 (m, 2H), 1.06 (s, 9H), 0.96 (d, 2H, $J = 9.9$ Hz), 0.90–0.73 (m, 2H), 0.86 (d, 3H, $J = 6.6$ Hz), 0.84 (d, 3H, $J = 7.7$ Hz), 0.68 (d, 3H, $J = 7.1$ Hz). IR (neat, cm^{-1}): 3400–3150 (br), 3064, 2951, 2931, 2863, 1629, 1543, 1111, 703. LRMS (m/z (relative intensity)): 585 (M^+ , 10), 528 ($\text{M}^+-\text{C}_4\text{H}_9$, 100). HRMS calc. for $\text{C}_{38}\text{H}_{55}\text{NO}_2\text{Si}$: 585.4002, found: 585.4006. $[\alpha]_{\text{D}}^{20} = -39.3$ ($c = 2.76$, CHCl_3).

3.11. Synthesis of amine 50b

Amine **48** (823 mg, 1.79 mmol) was dissolved in CH_2Cl_2 (30 mL). Acryloyl chloride (52 μL , 0.518 mmol) and Et_3N (37 μL , 0.518 mmol) were added and the mixture was stirred 15 min at rt. The reaction mixture was quenched with a saturated solution of ammonium chloride. The two phases were separated and the aqueous phase was extracted twice with DCM. The organic phases were combined, washed once with brine, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. Flash chromatography on silica gel, eluting with hexanes and ethyl acetate (4:1) furnished a clear oil (182 mg, 82%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.66–7.59 (m, 4H), 7.47–7.32 (m, 6H), 6.25 (dd, 1H, $J = 17.0$, 1.6 Hz), 6.05 (dd, 1H, $J = 17.0$, 10.4 Hz), 5.80 (d, 1H, $J = 8.8$ Hz), 5.64 (dd, 1H, $J = 10.4$, 1.6 Hz), 5.50 (dd, 1H, $J = 15.4$, 5.0 Hz), 5.42 (dd, 1H, $J = 15.4$, 7.7 Hz), 4.68–4.59 (m, 1H), 3.74 (d, 2H, $J = 3.9$ Hz), 1.98–1.77 (m, 2H), 1.76–1.65 (m, 1H), 1.64–1.53 (m, 1H), 1.44–1.17 (m, 1H), 1.25 (s, 1H), 1.06 (s, 9H), 0.96 (d, 2H, $J = 10.4$ Hz), 0.93–0.75 (m, 2H), 0.86 (d, 3H, $J = 7.1$ Hz), 0.84 (d, 3H, $J = 7.7$ Hz), 0.69 (d, 3H, $J = 6.6$ Hz). IR (neat, cm^{-1}): 3345–3185 (br), 2952, 2924, 2860, 1657, 1543, 1111, 703. LRMS (m/z (relative intensity)): 517 (M^+ , 5), 460 ($\text{M}^+-\text{C}_4\text{H}_9$, 100), 252 (65). HRMS calc. for $\text{C}_{33}\text{H}_{47}\text{NO}_2\text{Si}$: 517.3376, found: 517.3393. $[\alpha]_{\text{D}}^{20} = -42.4$ ($c = 6.70$, CHCl_3).

3.12. Synthesis of lactam 51

Amide **50a** (34 mg, 0.058 mmol) or **50b** (30 mg, 0.058 mmol) was dissolved in DCM (12 mL, concentration: 0.005 M). Argon was bubbled through the mixture for 15 min and then the solution was heated to reflux. The reflux was stopped and then the second generation Grubbs catalyst (2.5 mg, 0.0029 mmol, 5 mol%) was added to the reaction mixture. The reaction was stirred at reflux of DCM for 1 h (**50b**) or 10 min (**50a**). The solvent was evaporated and the crude product was purified by flash chromatography on a silica gel column eluting with hexanes and ethyl acetate (1:1) to give lactam **51** as a colorless oil (17 mg, 85% from **50a**, 19 mg, 92% from **50b**). ^1H NMR (CDCl_3 , 300 MHz): 7.67–7.60 (m, 4H), 7.51–7.35 (m, 6H), 7.02 (d, 1H, $J = 5.0$ Hz), 6.41 (br s, 1H), 6.13 (d, 1H, $J = 5.5$ Hz), 4.34 (t, 1H, $J = 6.5$ Hz), 3.77 (dd, 1H, $J = 9.9$, 5.0 Hz), 3.57 (dd, 1H, $J = 9.9$, 8.2 Hz) 1.06 (s, 9H). ^{13}C NMR (CDCl_3 , 75 MHz): 173.8 (s), 146.7 (d), 135.5 (d), 132.7 (s), 130.0 (d), 128.6 (d), 127.8 (d), 65.1 (t), 61.7 (d), 26.7 (q), 19.2 (s). IR (neat, cm^{-1}): 3639–3040 (br), 2936, 2860, 1696, 1111, 704. LRMS (m/z (relative intensity)): 351 (M^+ , 20), 294 (40), 199 (100), 84 (95). HRMS calc. for $\text{C}_{21}\text{H}_{25}\text{NO}_2\text{Si}$: 351.1654, found: 351.1658. $[\alpha]_{\text{D}}^{20} = +10.6$ ($c = 1.10$, CHCl_3).

3.13. Synthesis of amide 53a

Vinylmagnesium bromide (1.0 M in THF, 0.42 ml, 0.42 mmol) was added dropwise to a solution of the isocy-

anate (207 mg, 0.34 mmol) in THF (2.3 ml) at 0 °C. The solution was stirred at 0 °C for 2 h before quenching with saturated aqueous NH₄Cl (15 ml). The layers were separated and the aqueous layer was extracted with 3 × 15 mL of Et₂O. The organic layers were combined, washed with brine, dried with MgSO₄, filtered and evaporated. The crude compound was purified by flash chromatography eluting with Et₂O/hexanes (15:85) to yield 140 mg (65%) of the desired compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.33–7.24 (m, 5H), 6.21 (dd, 1H, *J* = 16.8, 1.7 Hz), 6.06 (dd, 1H, *J* = 16.8, 9.9 Hz), 5.57 (dd, 1H, *J* = 9.9, 1.7 Hz), 5.36 (d, 1H, *J* = 15.9 Hz), 5.38 (s, 1H), 5.17 (dd, 1H, *J* = 15.9, 8.8 Hz), 4.48 (s, 2H), 3.70–3.57 (m, 2H), 3.44 (t, 2H, *J* = 6.9 Hz), 2.27–2.05 (m, 2H), 1.98–1.17 (m, 16H), 1.13–0.95 (m, 21H), 0.92–0.80 (m, 2H), 0.86 (d, 6H, *J* = 6.6 Hz), 0.69 (d, 3H, *J* = 7.1 Hz). IR (neat) ν (cm⁻¹) 3379–3211 (br), 3022, 2946, 2865, 1660, 1549, 1457, 1103. LRMS (*m/z*, relative intensity) 625 (M⁺, 5), 582 ([M–C₃H₇]⁺, 57), 91 (100). HRMS calc. for C₃₉H₆₇NO₃Si: 625.4890, found: 625.4878. [α]_D²⁰ – 26.8 (*c* = 1.14, CHCl₃).

3.14. Synthesis of amide 53b

To a solution of isocyanate **38b** (44 mg, 0.16 mmol) in THF (1.1 mL, 0.15 M) at 0 °C was added vinyl magnesium bromide (0.85 M in THF, 0.2 mL, 0.17 mmol). The solution was stirred at 0 °C for 2 h. The reaction mixture was then poured over a saturated aqueous solution of ammonium chloride. The solution was extracted three times with diethyl ether (5 mL). Organic layers were combined, washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (30% of diethyl ether in hexanes) to yield pure acrylamide **53b** (46 mg, 96%, colorless oil). ¹H NMR (300 MHz, CDCl₃) δ 6.22 (dd, 1H, *J* = 17.1 Hz, 1.7 Hz), 6.04 (dd, 1H, *J* = 17.1 Hz, 9.9 Hz), 5.59 (d, 1H, *J* = 15.9 Hz), 5.56 (dd, 1H, *J* = 9.9 Hz, 1.7 Hz), 5.37 (s, 1H), 5.25 (dd, 1H, *J* = 16.0 Hz, 9.4 Hz), 1.95–1.65 (m, 5H), 1.62–1.56 (m, 2H), 1.44 (s, 3H), 1.42–1.16 (m, 3H), 1.06–0.75 (m, 7H), 0.86 (d, 3H, *J* = 7.2 Hz), 0.85 (d, 3H, *J* = 6.6 Hz), 0.69 (d, 3H, *J* = 7.1 Hz). ¹³C NMR (75.5 MHz, CDCl₃) δ 164.4 (s), 134.1 (d), 133.4 (d), 132.1 (d), 125.5 (t), 57.0 (s), 47.2 (d), 44.7 (d), 43.2 (t), 42.0 (t), 35.1 (t), 32.4 (d), 28.1 (d), 24.6 (q), 24.0 (t), 22.5 (q), 21.4 (q), 17.3 (t), 15.2 (q), 14.4 (q). IR (neat, cm⁻¹) 3287, 3063, 2956, 2928, 2871, 2844, 1659, 1625, 1549. LRMS (*m/z*, relative intensity) 305 (M⁺, 9), 262 ((M–C₃H₇)⁺, 42), 124 (100). HRMS calc. for C₂₀H₃₅NO: 305.2718, found: 305.2712. [α]_D²⁰ = –77.7 (*c* = 0.91, CHCl₃).

3.15. Synthesis of lactam 52

Acrylamide **53b** (34.8 mg, 0.114 mmol) was dissolved in dichloroethane (23 mL, 0.005 M) and argon was bubbled through this solution for 15 min. The mixture was then

heated to reflux. The reflux was stopped and catalyst **9** (9.7 mg, 10 mol%) was added to the solution. The reaction mixture was heat to reflux for 1.5 h. Dichloroethane was then evaporated under reduced pressure. The resulting dark brown oil was purified by flash chromatography (80% ethyl acetate in hexanes) to yield pure dihydropyrrolone **52** (9.5 mg, 60%). ¹H NMR (300 MHz, CDCl₃) δ 6.93 (dd, 1H, *J* = 5.5 Hz, 1.7 Hz), 6.80 (br s, 1H), 5.96 (dd, 1H, *J* = 5.5 Hz, 1.1 Hz), 1.70–1.52 (m, 2H), 1.40–1.12 (m, 2H), 1.34 (s, 3H), 0.89 (t, 3H, *J* = 7.2 Hz). ¹³C NMR (75.5 MHz, CDCl₃) δ 173.1 (s), 155.6 (d), 125.2 (d), 64.3 (s), 40.9 (t), 24.2 (q), 17.6 (t), 14.2 (q). IR (neat, cm⁻¹) 3214, 2960, 2932, 2873, 1685, 817. LRMS (*m/z*, relative intensity) 139 (M⁺, 1), 124 ((M–CH₃)⁺, 3), 96 ((M–C₃H₇)⁺, 100). HRMS calc. for C₈H₁₃NO: 139.0997, found: 139.0992. [α]_D²⁰ = –51.2 (*c* = 0.87, CHCl₃).

3.16. Synthesis of lactam 54

The acrylamide **53a** (40.0 mg, 0.064 mmol) was dissolved in toluene (13 mL, 0.005 M) and argon was bubbled through this solution for 15 min. The solution was then brought to reflux and cooled down to room temperature. Grubbs second generation catalyst **9** (5.5 mg, 10 mol%) was then added to the solution. The resulting mixture was refluxed for 2 h. The solvent was then evaporated under vacuum and the crude product was purified by flash chromatography eluting with EtOAc/hexane (7:3) to yield 19.5 mg (66%) of the desired compound. ¹H NMR (300 MHz, CDCl₃) δ 7.34–7.28 (m, 5H), 6.88 (d, 1H, 6.1 Hz), 6.01 (d, 1H, *J* = 6.1 Hz), 5.86 (br, 1H), 4.48 (s, 2H), 3.66 (t, 2H, *J* = 6.1 Hz), 3.43 (t, 2H, *J* = 6.3 Hz), 1.76–1.06 (m, 13H), 1.06 (d, 18H, *J* = 3.9 Hz). ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm), 173.1 (s), 154.6 (d), 138.4 (s), 128.3 (d), 128.3 (d), 127.7 (d), 127.6 (d), 126.3 (d), 73.0 (t), 68.8 (t), 67.2 (s), 63.0 (t), 37.0 (t), 33.7 (t), 29.9 (t), 27.2 (d), 20.7 (t), 18.0 (q), 11.9 (d). IR (neat) ν (cm⁻¹) 3375–3141 (br), 3062, 3035, 2941, 2865, 1694, 1461, 1099. LRMS (*m/z*, relative intensity) 416 ((M–C₃H₇)⁺, 100), 91 (40). HRMS calc. for C₂₄H₃₈O₃Si (M–C₃H₇): 416.2621, found: 416.2607. [α]_D²⁰ = 6.9° (*c* = 0.57, CHCl₃).

3.17. Synthesis of amide 55a

Isopropenylmagnesium bromide (0.5 M in THF, 1.40 mL, 0.70 mmol) was added dropwise to a solution of the isocyanate **38a** (348 mg, 0.58 mmol) in THF (5 mL) at 0 °C. The solution was stirred at 0 °C for 2 h before quenching with saturated aqueous NH₄Cl (20 mL). The layers were separated and the aqueous layer was extracted with 3 × 20 mL of Et₂O. The organic layers were combined, washed with brine, dried with MgSO₄, filtered and evaporated. The crude compound was purified by flash chromatography eluting with Et₂O/hexanes (15:85) to yield 351 mg (94%) of the desired compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.36–7.24 (m, 5H), 5.62 (s, 1H), 5.58 (s, 1H), 5.35 (d, 1H, *J* = 15.9 Hz), 5.26 (s, 1H), 5.17 (dd,

1H, $J = 15.9, 8.8$ Hz), 4.48 (s, 2H), 3.70–3.57 (m, 2H), 3.44 (t, 2H, $J = 6.6$ Hz), 2.20–2.06 (m, 2H), 1.98–1.55 (m, 9H), 1.93 (s, 3H), 1.51–1.20 (m, 5H), 1.13–0.96 (m, 23H), 0.97–0.80 (m, 2H), 0.86 (d, 6H, $J = 6.6$ Hz), 0.69 (d, 3H, $J = 6.6$ Hz). IR (neat) ν (cm^{-1}) 3474–3266 (br), 3027, 2944, 2865, 1677, 1629, 1497, 1454, 1103. LRMS (m/z , relative intensity) 639 (M^+ , 13), 596 ($[\text{M}-\text{C}_3\text{H}_7]$, 100), 476 (36). HRMS calc. for $\text{C}_{40}\text{H}_{69}\text{NO}_3\text{Si}$: 639.5046, found: 639.5058. $[\alpha]_{\text{D}}^{20} - 20.6$ ($c = 0.81$, CHCl_3).

3.18. Synthesis of amide 55b

A solution of amine **39a** (95 mg, 0.17 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a 0 °C suspension of 2-methylocta-2,7-dienoic acid (39 mg, 0.25 mmol), DCC (53 mg, 0.26 mmol) and DMAP (5.0 mg, 0.041 mmol) in CH_2Cl_2 (2 mL). The resulting white suspension was allowed to slowly warm up to room temperature while stirring for 48 h before quenching with saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with 3×15 mL of Et_2O . The organic layers were combined, washed with brine, dried with MgSO_4 , filtered and evaporated. The crude compound was purified by flash chromatography eluting with Et_2O /hexanes (20:80) to yield 60 mg (51%) of the desired compound as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.36–7.24 (m, 5H), 6.24 (t, 1H $J = 7.2$ Hz), 5.80 (ddt, 1H, $J = 17.1, 10.5, 6.6$ Hz), 5.52 (s, 1H), 5.36 (d, 1H, $J = 15.9$ Hz), 5.17 (dd, 1H, $J = 15.9, 9.8$ Hz), 5.02 (dd, 1H, $J = 17.1, 1.7$ Hz), 4.98 (dd, 1H, $J = 10.5, 1.7$ Hz), 4.48 (s, 2H), 3.70–3.56 (m, 2H), 3.43 (t, 2H, $J = 6.6$ Hz), 2.21–2.04 (m, 6H), 1.99–1.15 (m, 16H), 1.81 (s, 3H), 1.13–0.95 (m, 22H), 0.92–0.79 (m, 3H), 0.86 (d, 6H, $J = 7.2$ Hz), 0.70 (d, 3H, $J = 6.6$ Hz). IR (neat) ν (cm^{-1}) 3477–3265 (br), 3074, 3032, 2943, 2865, 1672, 1638, 1497, 1463, 1103. LRMS (m/z , relative intensity) 707 (M^+ , 12), 664 ($[\text{M}-\text{C}_3\text{H}_7]^+$, 100), 544 (48), 492 (42), 91 (66). HRMS calc. for $\text{C}_{45}\text{H}_{77}\text{NO}_3\text{Si}$: 707.5672, found: 707.5681. $[\alpha]_{\text{D}}^{20} - 28.5$ ($c = 0.66$, CHCl_3).

3.19. Synthesis of amide 55c

A solution of amine **39a** (70 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a 0 °C suspension of 2-methylnona-2,7-dienoic acid (31 mg, 0.18 mmol), DCC (37 mg, 0.18 mmol) and DMAP (4.0 mg, 0.033 mmol) in CH_2Cl_2 (2 mL). The resulting white suspension was allowed to slowly warm up to room temperature while stirring for six days before quenching with saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with 3×15 mL of Et_2O . The organic layers were combined, washed with brine, dried with MgSO_4 , filtered and evaporated. The crude compound was purified by flash chromatography eluting with Et_2O /hexanes (10:90) to yield 31 mg (36%) of the desired compound as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.33–7.24 (m, 5H), 6.23 (t, 1H $J = 7.4$ Hz), 5.52 (s, 1H), 5.46–5.41 (m, 2H), 5.35 (d, 1H, $J = 15.9$ Hz), 5.16 (dd, 1H,

$J = 15.9, 8.8$ Hz), 4.47 (s, 2H), 3.70–3.56 (m, 2H), 3.43 (t, 2H, $J = 6.6$ Hz), 2.20–2.00 (m, 6H), 1.99–1.22 (m, 20H), 1.81 (s, 3H), 1.12–0.96 (m, 22H), 0.92–0.79 (m, 2H), 0.86 (d, 6H, $J = 7.2$ Hz), 0.70 (d, 3H, $J = 7.2$ Hz). IR (neat) ν (cm^{-1}) 3458–3261 (br), 3017, 2943, 2865, 1672, 1638, 1496, 1455, 1103. LRMS (m/z , relative intensity) 721 (M^+ , 10), 678 ($[\text{M}-\text{C}_3\text{H}_7]^+$, 100), 558 (48), 91 (78). HRMS calc. for $\text{C}_{46}\text{H}_{79}\text{NO}_3\text{Si}$: 721.5829, found: 721.5834. $[\alpha]_{\text{D}}^{20} - 23.9$ ($c = 1.12$, CHCl_3).

3.20. Synthesis of lactam 56

A toluene (12.8 mL) solution of methylacrylamide **55c** (22.9 mg, 0.032 mmol), in which argon had been bubbled for 15 min, was slowly added over a period of 30 min to a refluxing toluene (6.4 mL) solution of catalyst **9** (2.7 mg, 10 mol%). The resulting mixture was further refluxed for 30 min while continuously bubbling argon through the reaction. The solvent was then evaporated under vacuum and the crude product was purified by flash chromatography eluting with EtOAc /hexane (4:6) to yield 13.6 mg (91%) of the desired compound. ^1H NMR (300 MHz, CDCl_3) δ 7.37–7.25 (m, 5H), 6.49 (s, 1H), 5.80 (s, 1H), 4.48 (s, 2H), 3.63 (t, 2H, $J = 6.0$ Hz), 3.42 (t, 2H, $J = 6.3$ Hz), 1.86 (s, 3H), 1.70–1.18 (m, 11H), 1.10–0.99 (m, 20H). ^{13}C NMR (75.5 MHz, CDCl_3) δ 173.7 (s), 147.0 (d), 138.4 (s), 133.8 (s), 128.4 (d), 127.7 (d), 127.5 (d), 72.9 (t), 69.9 (t), 64.1 (s), 63.2 (t), 37.4 (t), 33.9 (t), 29.9 (t), 27.4 (t), 20.7 (q), 18.0 (q), 11.9 (d), 10.7 (q). IR (neat) ν (cm^{-1}) 3375–3132 (br), 3061, 3032, 2942, 2865, 1694, 1103. LRMS (m/z , relative intensity) 473 (M^+ , 1), 430 ($[\text{M}-\text{C}_3\text{H}_7]^+$, 100), 91 (17). HRMS calc. for $\text{C}_{28}\text{H}_{47}\text{O}_3\text{Si}$: 473.3325, found: 473.3317. $[\alpha]_{\text{D}}^{20} - 7.1^\circ$ ($c = 1.34$, CHCl_3).

3.21. Synthesis of amide 58a

Prepared as per amide **50a**. Colorless oil (300 mg, 87%). ^1H NMR (300 MHz, CDCl_3) δ 7.70–7.68 (m, 4H), 7.42–7.35 (m, 6H), 5.98–5.91 (m, 1H), 5.89–5.79 (m, 1H), 5.44–5.17 (m, 3H), 4.45–4.38 (m, 1H), 3.68 (t, 3H, $J = 6.0$ Hz), 2.99 (d, 2H, $J = 7.2$ Hz), 1.87–1.3 (m, 10H), 1.08 (s, 9H), 1.04–0.84 (m, 12H), 0.71 (d, 3H, $J = 7.2$ Hz). ^{13}C NMR (75.5 MHz, CDCl_3) δ 169.5 (s) 136.6 (d), 135.6 (d), 134.0 (s), 131.7 (d), 129.5 (d), 127.6 (d), 119.2 (t), 63.7 (t), 50.9 (d), 47.2 (d), 44.5 (d), 43.0 (t), 41.8 (t), 35.1 (t), 35.0 (t), 32.6 (t), 28.0 (d), 26.9 (q), 24.1 (t), 22.7 (q), 22.2 (t), 21.4 (t), 19.2 (s), 15.4 (q). IR (neat, NaCl): cm^{-1} 3276; 3069; 2957; 2927; 2863; 1647; 1115. LRMS (m/z relative intensity): 573 (M^+ , 8), 516 (100), 266 (40), 199 (30). HRMS calc. for: $\text{C}_{37}\text{H}_{55}\text{NO}_2\text{Si}$: 573.4002; found: 573.4016.

3.22. Synthesis of amide 58b

Prepared as per amide **53b**. Colorless oil (125 mg, 99%). ^1H NMR (300 MHz, CDCl_3) δ 5.92 (ddt, 1H, $J = 17.1, 9.9,$

1.7 Hz), 5.52 (d, 2H, $J = 15.4$ Hz), 5.40 (bs, 1H), 5.20 (dd, 1H, $J = 15.4, 9.4$ Hz), 5.23–5.17 (m, 2H), 2.93 (d, 2H, $J = 7.2$ Hz), 1.93–1.55 (m, 7H), 1.39 (s, 3H), 1.43–1.26 (m, 1H), 1.24–1.13 (m, 2H), 1.06–0.77 (m, 9H), 0.86 (d, 3H, $J = 7.2$ Hz), 0.69 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (75.5 MHz, CDCl_3) δ 169.3 (s), 134.6 (d), 133.2 (d), 132.1 (d), 119.3 (t), 56.8 (s), 47.2 (d), 44.7 (d), 43.2 (t), 42.8 (t), 41.9 (t), 35.1 (t), 32.4 (d), 28.1 (d), 24.7 (q), 24.1 (t), 22.5 (q), 21.4 (q), 17.3 (t), 15.2 (q), 14.3 (q). IR (neat/ NaCl) ν (cm^{-1}) 3297, 3077, 2955, 2928, 2871, 1650, 1546. LRMS (m/z , relative intensity) 320 (MH^+ , 86), 319 (M^+ , 74), 276 ($\text{M}^+ - \text{C}_3\text{H}_7$, 97), 191 (62), 154 (61), 138 (100), 86 (99). HRMS calc. for $\text{C}_{21}\text{H}_{37}\text{NO}$: 319.2875, found: 319.2868. $[\alpha]_{\text{D}}^{20} = -68.9$ ($c = 0.93$, CHCl_3).

3.23. Synthesis of amide 58c

Prepared as per amide **53b**. White solid (124 mg, 85%); m.p.: 41–42 °C; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 5.83 (ddt, 1H, $J = 17.0, 10.5, 6.6$ Hz), 5.39–5.24 (m, 3H), 5.07 (dd, 1H, $J = 17.0, 1.7$ Hz), 5.01 (d, 1H, $J = 10.5$ Hz), 4.47–4.38 (m, 1H), 2.40 (dt, 2H, $J = 6.6, 7.1$ Hz), 2.28–2.24 (m, 2H), 1.91–1.68 (m, 3H), 1.63–1.49 (m, 2H), 1.47–1.42 (m, 2H), 1.39–1.25 (m, 2H), 1.01–0.77 (m, 5H), 0.91 (t, 3H, $J = 7.7$ Hz), 0.86 (d, 6H, $J = 6.6$ Hz), 0.68 (d, 3H, $J = 7.1$ Hz). ^{13}C NMR (75.5 MHz, CDCl_3) δ (ppm) 171.1 (s), 137.1 (d), 136.4 (d), 129.2 (d), 115.4 (t), 50.5 (d), 47.0 (d), 44.5 (d), 43.2 (t), 37.7 (t), 36.0 (t), 35.1 (t), 32.4 (d), 29.7 (t), 28.0 (d), 24.0 (t), 22.5 (q), 21.4 (q), 19.0 (t), 15.2 (q), 13.9 (q). IR (neat, cm^{-1}) 3277 (br), 3077, 2955, 2918, 2870, 2849, 1640, 1547. LRMS (m/z , relative intensity) 319 (M^+ , 34), 276 ($(\text{M} - \text{C}_3\text{H}_7)^+$, 55), 180 (68), 138 (74), 98 (100). HRMS calc. for $\text{C}_{21}\text{H}_{37}\text{NO}$: 319.2875, found: 319.2870. $[\alpha]_{\text{D}}^{20} = -16.6$ ($c = 1.04$, CHCl_3).

3.24. Synthesis of lactam 59a

In a 25 mL round-bottomed flask was added amide **58a** (200 mg, 0.35 mmol) and dichloromethane (70 mL). The solution was heated to reflux and then it was degassed by bubbling argon for 15 min. Then the heating was briefly stopped and dichlorophenylborane (35 μL , 0.35 mmol) was added followed by catalyst **9** (29 mg, 0.034 mmol) was added to the warm solution. The solution was heated to reflux for 3 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography on silica gel (60% EtOAc/dichloromethane) to afford 110 mg of pyridone **59a** (77%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.66 (dd, 4H, $J = 7.7$ Hz, 1.9 Hz), 7.56–7.26 (m, 6H), 6.60 (br s, 1H), 5.75 (d, 1H, $J = 10.4$ Hz), 5.65 (d, 1H, $J = 10.6$ Hz), 4.10–3.98 (m, 1H), 3.66 (t, 2H, $J = 6.3$ Hz), 2.93–2.85 (m, 2H), 1.62–1.50 (m, 4H), 1.46–1.37 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl_3) δ (ppm) 169.7 (s), 135.6 (d), 133.9 (s), 129.5 (d), 127.6 (d), 125.3 (d), 121.7 (d), 63.5 (t), 53.8 (d), 36.8 (t), 32.2 (t), 26.9 (q), 20.8 (t), 19.1 (s). IR (neat, NaCl): cm^{-1} : 3201; 3071; 3039; 2931; 2853;

1674; 1659; 1109. LRMS (m/z relative intensity): 350 ($(\text{M} - \text{C}_4\text{H}_9)^+$, 80), 272 (100), 199 (45), 96 (550). HRMS calc. for $\text{C}_{25}\text{H}_{33}\text{NO}_2\text{Si}$: 350.1576; found: 350.1578.

3.25. Synthesis of lactam 59b

The amide **58b** (22 mg, 0.068 mmol) was dissolved in dichloroethane (13 mL, 0.005 M), heat to reflux, and argon was bubbled through this solution for 15 min. The reflux was stopped and dichlorophenylborane (8 μL , 0.068 mmol) and catalyst **9** (5.0 mg, 10 mol%) was added to the solution. The reaction mixture was heat to reflux for 2 h. Dichloroethane was then evaporated under reduced pressure. The resulting dark brown oil was purified by flash chromatography (80% ethyl acetate in hexanes) to yield pure dihydropyridinone **59b** (8.4 mg, 79%); m.p.: 86–87 °C; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 6.19 (s(br), 1H), 5.70 (dt, 1H, $J = 10.5, 3.3$ Hz), 5.52 (dq, 1H, $J = 10.5, 2.2$ Hz), 2.87 (dd, 2H, $J = 3.3, 2.2$ Hz), 1.56–1.40 (m, 2H), 1.38–1.18 (m, 2H), 1.29 (s, 3H), 0.88 (t, 3H, $J = 7.4$ Hz). ^{13}C NMR (75.5 MHz, CDCl_3) δ (ppm) 169.7 (s), 130.3 (d), 120.3 (d), 57.9 (s), 45.4 (t), 30.8 (t), 29.9 (q), 17.2 (t), 14.0 (q). IR ($\text{CHCl}_3/\text{NaCl}$) ν (cm^{-1}) 3201, 3154, 3033, 2959, 2933, 2910, 2873, 1678, 1661, 1446, 1400, 1153. LRMS (m/z , relative intensity) 153 (M^+ , 1), 138 ($(\text{M} - \text{CH}_3)^+$, 27), 110 ($(\text{M} - \text{C}_3\text{H}_7)^+$, 100). HRMS calc. for $\text{C}_9\text{H}_{15}\text{NO}$: 153.1154, found: 153.1156. $[\alpha]_{\text{D}}^{20} = -59.1$ ($c = 1.52$, CHCl_3).

3.26. Synthesis of lactam 57c

Prepared as per lactam **59b**. Colorless oil (2.9 mg, 30%). ^1H NMR (300 MHz, CDCl_3) δ 6.60 (ddd, 1H, $J = 9.9, 5.5, 3.3$ Hz), 5.91 (d, 1H, $J = 9.9$ Hz), 5.42 (s(br), 1H), 3.60 (sext., 1H, $J = 6.0$ Hz), 2.38 (dt, 2H, $J = 17.6, 5.5$ Hz), 2.14 (ddt, 1H, $J = 17.6, 11.0, 3.3$ Hz), 1.60–1.45 (m, 3H), 1.42–1.21 (m, 2H), 0.95 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (75.5 MHz, CDCl_3) δ 169.2 (s), 140.7 (d), 124.4 (d), 50.8 (d), 46.3 (t), 37.5 (t), 30.0 (t), 18.5 (t), 13.8 (q). IR ($\text{CHCl}_3/\text{NaCl}$) ν (cm^{-1}) 3223, 2959, 2929, 2874, 1678, 1612. LRMS (m/z , relative intensity) 153 (M^+ , 3), 138 ($(\text{M} - \text{CH}_3)^+$, 3), 110 ($(\text{M} - \text{C}_3\text{H}_7)^+$, 20), 96 (100). HRMS calc. for $\text{C}_9\text{H}_{15}\text{NO}$: 153.1154, found: 153.1150. $[\alpha]_{\text{D}}^{20} = -89.2$ ($c = 0.10$, CHCl_3).

3.27. Synthesis of carbamate 60

Prepared by the same procedure as per carbamate **35b**, except in this case, the reaction was stopped after 30 h. Colorless oil (969 mg, 83%). ^1H NMR (CDCl_3 , 300 MHz) δ 5.84–5.70 (m, 1H), 5.60–5.25 (m, 2H), 4.99 (d, 1H, $J = 17.0$ Hz), 4.95 (d, 1H, $J = 9.3$ Hz), 4.45–4.18 (m, 1H), 3.30–3.15 (m, 1H), 3.00–2.80 (m, 1H), 2.00–1.27 (m, 12H), 1.45 (s, 9H), 1.10–0.76 (m, 9H), 0.88 (s, 9H), 0.69 (d, 3H, $J = 6.6$ Hz). IR (neat, cm^{-1}): 3082, 2920, 1696, 1453, 1174. LRMS (m/z (relative intensity)): 362

($M^+ - C_4H_9$, 15), 306 (100), 262 (30). HRMS calc. for $C_{23}H_{40}NO_2$: 362.3059, found: 362.3064. $[\alpha]_D^{20} = -28.2$ ($c = 1.60$, $CHCl_3$).

3.28. Syntheses of *S*-thiocarbamate **64a–b**. General procedure

To a solution of the allylic alcohol **63a** or **b** (1 eq) in THF at 0 °C was added NaH 60% w/w in oil (1.9 eq) and the mixture was stirred for 1 h at this temperature before the addition of phenylisothiocyanate (2 eq). The reaction was heated to reflux and stirred for 3 h. It was then cooled down to rt before the addition of pyridinium *p*-toluenesulfonate (2.5 eq) in THF. The reaction was then heated to reflux and monitored by TLC. When the reaction was complete, it was stopped by the addition of a 1:1 mixture of water and Et_2O . The two phases were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate.

3.28.1. *S*-Thiocarbamate **64a**

White solid (97%, 97% de by GC); m.p. 72–74 °C; 1H NMR: (300 MHz, $CDCl_3$): δ 7.44 (t, 2H, $J = 8.3$ Hz), 7.28 (t, 2H, $J = 7.7$ Hz), 7.10–1.05 (m, 1H), 5.50 (dd, 1H, $J = 15.4$, 8.8 Hz), 5.39 (dd, 1H, $J = 15.4$, 8.3 Hz), 4.13–4.05 (m, 1H), 1.93–1.56 (m, 7H), 1.47–1.33 (m, 4H), 1.02–0.76 (m, 6H), 0.92 (d, 3H, $J = 7.2$ Hz), 0.88 (d, 3H, $J = 7.2$ Hz), 0.71 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4 (s), 137.9 (s), 137.8 (d), 129.0 (d), 128.6 (d), 124.2 (d), 119.8 (d), 47.6 (d), 47.0 (d), 44.6 (d), 42.9 (t), 37.5 (t), 35.1 (t), 32.4 (d), 28.2 (d), 24.1 (t), 22.5 (q), 21.4 (q), 20.5 (t), 15.3 (q), 13.7 (q); IR (neat, cm^{-1}): 3297, 2956, 2927, 2871, 1656, 1600, 1440, 1309, 750; LRMS (m/z (relative intensity)): 373 (M^+ , 8), 270 (10), 221 (65), 83 (100); Exact Mass calc. for $C_{23}H_{35}ONS$: 373.2439, found: 373.2448; $[\alpha]_D^{20} = +42.5$ (c 1.02, $CHCl_3$).

3.28.2. *S*-Thiocarbamate **64b**

White solid (96%, 98.5% de by GC); m.p. 102–103 °C; 1H NMR: (300 MHz, $CDCl_3$): δ 7.41 (d, 2H, $J = 8.3$ Hz), 7.30 (t, 2H, $J = 8.0$ Hz), 7.11–7.07 (m, 2H), 5.50–5.47 (m, 2H), 3.97–3.94 (m, 1H), 1.91–1.78 (m, 2H), 1.70 (d, 1H, $J = 12.1$ Hz), 1.62–1.53 (m, 2H), 1.36–1.21 (m, 1H), 1.01 (s, 9H), 0.98–0.78 (m, 4H), 0.85 (d, 3H, $J = 7.2$ Hz), 0.82 (d, 3H, $J = 6.6$ Hz), 0.70 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1 (s), 138.1 (d), 137.9 (s), 129.0 (d), 127.0 (d), 124.1 (d), 119.5 (d), 59.9 (d), 47.0 (s), 44.9 (d), 42.9 (t), 35.1 (t), 34.4 (d), 32.5 (d), 28.2 (d), 27.9 (q), 23.9 (t), 22.5 (q), 21.4 (q), 15.1 (q); IR (neat, cm^{-1}): 3298, 2958, 2922, 2869, 1659, 1440, 1143, 750; LRMS (m/z (relative intensity)): 387 (M^+ , 5), 330 (3), 177 (64), 97 (100); Exact Mass calc. for $C_{24}H_{37}ONS$: 387.2596; Found: 387.2591; $[\alpha]_D^{20} = -118.7$ (c 1.31, $CHCl_3$).

3.29. Synthesis of sulfides **65a–c**: general procedure

The thiocarbamate (1 eq) and the alkyl bromide (5 eq) were solubilized in of methanol and cesium carbonate (5 eq) was added. The mixture was stirred and heated at 80 °C in a sealed tube for 4 h. A 1:1 mixture of water and diethyl ether were added to the reaction mixture. The two layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate.

3.29.1. Sulfide **65a**

Colorless oil (69% yield). 1H NMR: (300 MHz, $CDCl_3$): δ 5.79 (dddd, 1H, $J = 10.2$, 8.5, 8.5, 6.3 Hz), 5.16–5.05 (m, 4H), 3.17–3.00 (m, 3H), 2.04–1.80 (m, 2H), 1.79–1.29 (m, 11H), 1.02–0.67 (m, 4H), 0.87 (d, 6H, $J = 6.6$ Hz), 0.70 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5 (d), 135.1 (d), 130.1 (d), 116.5 (t), 47.1 (d), 46.3 (d), 44.8 (d), 43.9 (t), 36.6 (t), 35.1 (t), 33.2 (t), 32.5 (d), 28.2 (d), 23.9 (t), 22.6 (q), 21.4 (q), 20.6 (t), 15.1 (q), 13.7 (q); IR (neat, cm^{-1}): 3075, 2951, 2869, 1635, 1458, 1369; LRMS (m/z (relative intensity)): 294 (M^+ , 3), 220 (80), 137 (100); Exact Mass calc. for $C_{19}H_{34}S$: 294.2381, found: 294.2376; $[\alpha]_D^{20} = -5.7$ (c 1.18, $CHCl_3$).

3.29.2. Sulfide **65b**

Colorless oil (79% yield). 1H NMR: (300 MHz, $CDCl_3$): δ 5.76 (dddd, 1H, $J = 16.5$, 10.7, 8.4, 5.9 Hz), 5.31 (dd, 1H, $J = 14.8$, 10.4 Hz), 5.12–5.04 (m, 3H), 3.07 (dd, 1H, $J = 13.8$, 5.5 Hz), 2.99 (dd, 1H, $J = 14.0$, 8.5 Hz), 2.83 (d, 1H, $J = 9.9$ Hz), 2.03–1.56 (m, 4H), 1.43–1.32 (m, 1H), 1.25–0.67 (m, 11H), 0.97 (s, 9H), 0.71 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6 (d), 135.2 (d), 127.5 (d), 116.5 (t), 58.8 (d), 47.2 (d), 45.2 (d), 44.2 (t), 35.1 (t), 33.8 (t), 33.2 (s), 32.6 (d), 28.2 (q), 28.1 (d), 23.8 (t), 22.6 (q), 21.4 (q), 15.0 (q); IR (neat, cm^{-1}): 2955, 2920, 2871, 1458, 1366, 971, 912; LRMS (m/z (relative intensity)): 308 (M^+ , 6), 267 ($(M - C_3H_5)^+$, 24), 257 ($(M - C_4H_9)^+$, 100), 177 (78), 97 (88); Exact Mass calc. for $C_{20}H_{36}S$: 308.2538, found: 308.2543; $[\alpha]_D^{20} = +9.6$ (c 1.31, $CHCl_3$).

3.29.3. Sulfide **65c**

Colorless oil (75% yield). 1H NMR: (300 MHz, $CDCl_3$): δ 5.82 (ddt, 1H, $J = 16.8$, 10.3, 6.6 Hz), 5.31 (dd, 1H, $J = 15.1$, 10.2 Hz), 5.15–5.07 (m, 2H), 5.02–4.99 (m, 1H), 2.88 (d, 1H, $J = 10.4$ Hz), 2.48–2.38 (m, 2H), 2.36–2.21 (m, 2H), 1.98–1.80 (m, 2H), 1.74–1.70 (m, 1H), 1.65–1.56 (m, 3H), 1.40–1.25 (m, 1H), 0.98–0.77 (m, 3H), 0.97 (s, 9H), 0.87 (d, 3H, $J = 7.2$ Hz), 0.86 (d, 3H, $J = 6.6$ Hz), 0.71 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.3 (d), 137.1 (d), 127.6 (d), 115.5 (t), 60.1 (d), 47.2 (d), 45.0 (d), 44.0 (s), 35.1 (t), 34.0 (t), 33.8 (q), 32.5 (d), 29.8 (t), 28.2 (d), 28.0 (q), 23.9 (t), 22.5 (q), 21.4 (t), 15.0 (q);

IR (neat, cm^{-1}): 2955, 2917, 2870, 1517, 1457; LRMS (m/z (relative intensity)): 322 (M^+ , 28), 265 (98), 205 (69), 177 (72), 127 (100); Exact Mass calc. for $\text{C}_{21}\text{H}_{38}\text{S}$: 322.2694, found: 322.2705; $[\alpha]_{\text{D}}^{20} = -12.3$ (c 0.86, CHCl_3).

3.30. Synthesis of sulfones **66a–c**: general procedure

The allylic sulfide (1 eq) was solubilized in dry dichloromethane and *m*-chloroperbenzoic acid (60%) (2 eq) was added to the solution. The mixture was stirred for 10 min. at rt and was then cooled to 0 °C before the addition of a 1:2:2 mixture of water, saturated aqueous solution of NaHCO_3 , and dichloromethane. The two layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with a mixture of hexanes and ethyl acetate.

3.30.1. Sulfone **66a**

Colorless oil (71% yield). ^1H NMR: (300 MHz, CDCl_3): δ 5.90 (dddd, 1H, $J = 10.2, 8.5, 8.5, 6.4$ Hz), 5.58–5.30 (m, 4H), 3.83 (dd, 1H, $J = 14.4, 8.5$ Hz), 3.59 (dd, 1H, $J = 14.4, 6.4$ Hz), 3.52 (td, 1H, $J = 10.5, 3.3$ Hz), 2.10–1.95 (m, 2H), 1.77–1.61 (m, 6H), 1.50–1.32 (m, 2H), 1.30–1.18 (m, 1H), 1.03–0.82 (m, 6H), 0.93 (d, 3H, $J = 7.7$ Hz), 0.88 (d, 3H, $J = 6.6$ Hz), 0.71 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 144.9 (d), 125.1 (d), 124.2 (t), 122.0 (d), 64.4 (d), 54.5 (t), 46.8 (d), 45.1 (d), 42.5 (t), 34.9 (t), 32.2 (d), 28.4 (d), 27.1 (t), 23.7 (t), 22.4 (q), 21.2 (q), 19.5 (t), 15.0 (q), 13.4 (q); IR (neat, cm^{-1}): 2957, 2927, 2872, 1312, 1290, 1132; LRMS (m/z (relative intensity)): 344 (MNH_4^+ , 42), 221 (100), 123 (20); Exact Mass calc. for $\text{C}_{19}\text{H}_{38}\text{NO}_2\text{S}$ (MNH_4^+): 344.2623, found: 344.2630; $[\alpha]_{\text{D}}^{20} = -48.7$ (c 0.86, CHCl_3).

3.30.2. Sulfone **66b**

White solid (77% yield); m.p. 108–109 °C. ^1H NMR: (300 MHz, CDCl_3): δ 5.88 (dddd, 1H, $J = 16.0, 10.5, 9.0, 6.1$ Hz), 5.60 (dd, 1H, $J = 15.1, 10.2$ Hz), 5.49–5.31 (m, 3H), 3.85 (dd, 1H, $J = 13.8, 9.0$ Hz), 3.41 (dd, 1H, $J = 13.8, 6.1$ Hz), 3.32 (d, 1H, $J = 10.5$ Hz), 2.11–2.00 (m, 1H), 1.76–1.59 (m, 4H), 1.43–1.17 (m, 1H), 1.14 (s, 9H), 1.05–0.78 (m, 4H), 0.86 (d, 3H, $J = 6.1$ Hz), 0.85 (d, 3H, $J = 7.7$ Hz), 0.69 (d, 3H, $J = 6.6$ Hz); IR (CHCl_3 , cm^{-1}): 3028, 2957, 1310, 1126; LRMS (m/z (relative intensity)): 358 (MNH_4^+ , 30), 235 (100), 97 (70); Exact Mass calc. for $\text{C}_{20}\text{H}_{40}\text{NO}_2\text{S}$ (MNH_4^+): 358.2780, found: 358.2784; $[\alpha]_{\text{D}}^{20} = -73.5$ (c 0.73, CHCl_3).

3.30.3. Sulfone **66c**

Colorless solid (99% yield); m.p. 102–103 °C. ^1H NMR: (300 MHz, CDCl_3): δ 5.78 (dddd, 1H, $J = 17.1, 10.5, 6.6, 6.6$ Hz), 5.62 (dd, 1H, $J = 15.4, 10.4$ Hz), 5.48 (dd, 1H, $J = 15.4, 9.4$ Hz), 5.13–5.07 (m, 2H), 3.35 (d, 1H, $J = 10.5$ Hz), 3.06 (ddd, 1H, $J = 13.8, 10.5, 6.0$ Hz), 2.93

(ddd, 1H, $J = 13.8, 10.5, 5.5$ Hz), 2.61–2.46 (m, 2H), 2.11–2.01 (m, 1H), 1.77–1.73 (m, 2H), 1.65–1.55 (m, 2H), 1.42–1.25 (m, 1H), 1.18 (s, 9H), 1.08–0.78 (m, 4H), 0.89 (d, 3H, $J = 7.2$ Hz), 0.87 (d, 3H, $J = 6.1$ Hz), 0.72 (d, 3H, $J = 6.6$ Hz); IR (neat, cm^{-1}): 2947, 2917, 2855, 1305, 1126; LRMS (m/z (relative intensity)): 372 (MNH_4^+ , 100), 235 (65); Exact Mass calc. for $\text{C}_{21}\text{H}_{42}\text{NO}_2\text{S}$ (MNH_4^+): 372.2936, found: 372.2942; $[\alpha]_{\text{D}}^{20} = -81.1$ (c 0.36, CHCl_3).

3.31. Synthesis of tetrahydrothiophene **67a**

Prepared as per tetrahydrothiophene **67b**. Analysis of the crude reaction mixture clearly show 97% conversion of **65a** to **67b** as well as auxiliary by-product **5**. However, any attempt to purify **67a** resulted in complete loss of this highly volatile material.

3.32. Synthesis of tetrahydrothiophene **67b**

A solution of sulfide **65b** (92 mg, 0.298 mmol) in dry dichloromethane (30 mL, 0.01 M), was heated to reflux and then degassed by passing a stream of argon for 15 min. while refluxing. Catalyst **21** (25 mg, 0.030 mmol) was quickly added while the solution was still under reflux. The resulting pale pink solution was refluxed for 18 h. It was cooled to rt and volatiles were removed under vacuum without heating. Analysis of the crude reaction mixture showed complete conversion to **67b** and auxiliary by-product **5**. The crude product was purified by flash chromatography on silica gel (100% pentane) to afford the desired product **67b** (36 mg, 85%) as a colorless oil. ^1H NMR: (300 MHz, CDCl_3): δ 5.86 (tdd, 1H, $J = 4.4, 2.2, 2.2$ Hz), 5.77 (tdd, 1H, $J = 4.4, 2.2, 2.2$ Hz), 4.12 (br s, 1H), 3.64 (br s, 2H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): δ 130.9 (d), 128.9 (d), 68.0 (d), 38.4 (t), 35.5 (s), 27.1 (q); IR (neat, cm^{-1}): 2956, 2868, 1712, 1691, 1463; LRMS (m/z (relative intensity)): 142 (M^+ , 20), 85 (100), 77 (10); Exact Mass calc. for $\text{C}_8\text{H}_{14}\text{S}$: 142.0816, found: 142.0814; $[\alpha]_{\text{D}}^{20} = -43.1$ (c 1.23, CHCl_3).

3.33. Synthesis of sulfolene **68a**

A solution of sulfone **66a** (54 mg, 0.166 mmol) in dry dichloromethane (165 mL, 0.001 M), was heated to reflux and then degassed by passing a stream of argon for 15 min. while refluxing. Catalyst **21** (10 mg, 0.012 mmol) was quickly added while the solution was still under reflux. The resulting pale pink solution was refluxed for 18 h. It was cooled to rt and volatiles were removed under vacuum without heating. The crude product was purified by flash chromatography on silica gel (100% hexanes/40% EtOAc/hexanes) to afford the desired product **68a** (27 mg, >99%) as a colorless oil. ^1H NMR: (300 MHz, CDCl_3): δ 6.02 (s, 2H), 3.79–3.64 (m, 3H), 2.04–1.86 (m, 1H), 1.68–1.45 (m, 3H), 0.99 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 130.4 (d), 122.9 (d), 64.2 (d), 55.5 (t), 30.6 (t), 20.3 (t), 13.8 (q); IR (neat, cm^{-1}): 3069, 2975, 2869, 1464,

1310, 1121; LRMS (m/z (relative intensity)): 178 (MNH_4^+ , 81), 161 (MH^+ , 20), 96 (100); Exact Mass calc. for $\text{C}_7\text{H}_{13}\text{SO}_2$ (MH^+): 161.0636, found: 161.0641; $[\alpha]_{\text{D}}^{20} = -21.7$ (c 2.38, CHCl_3).

3.34. Synthesis of sulfolene **68b**

Prepared as per sulfolene **68a** (21 mg, 84%) and the dimer of **66b** (7 mg), both as colorless oils. ^1H NMR: (300 MHz, CDCl_3): δ 6.17–6.06 (m, 2H), 3.74–3.56 (m, 2H), 3.55–3.53 (m, 1H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): δ 129.1 (d), 124.0 (d), 74.4 (d), 56.4 (t), 34.5 (s), 2.71 (q); IR (neat, cm^{-1}): 2963, 2868, 1298, 1245, 1109; LRMS (m/z (relative intensity)): 192 (MNH_4^+ , 40), 175 (MH^+ , 5), 110 (100); Exact Mass calc. for $\text{C}_8\text{H}_{15}\text{SO}_2$ (MH^+): 175.0793, found: 175.0790; $[\alpha]_{\text{D}}^{20} = -15.2$ (c 1.96, CHCl_3).

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