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An Alkylidene Carbene C−H Activation Approach toward the Enantioselective Syntheses of Spirolactams: Application to the Synthesis of (−)-Adalinine

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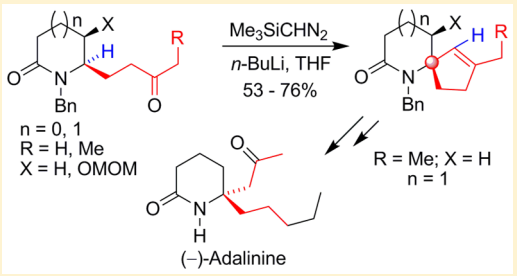
Supporting Information

ABSTRACT: A method based on *in situ* alkylidene carbene generation-C−H insertion reaction of 5-(3-oxobutyl)pyrrolidin-2-ones and 6-(3-oxobutyl)piperidin-2-ones is developed for the enantioselective synthesis of 1-azaspiro[4,4]non-6-ene-2-ones and 6-azaspiro[4,5]dec-1-ene-7-ones. The required 5-(3-oxobutyl)pyrrolidin-2-ones and 6-(3-oxobutyl)piperidin-2-ones are prepared from the Wacker oxidation of internal alkenes typified by 5-(but-2-enyl)pyrrolidin-2-ones and 6-(but-2-enyl)piperidin-2-ones, respectively. Excellent regioselectivity (≥92:8) is realized for the Wacker oxidation, and high yields (78−89%) of the desired lactam ketones are obtained. The results from further investigations into the Wacker oxidation suggested that the high regioselectivity of the oxidation in these lactam alkenes might be due to the participation of the lactam nitrogen via intramolecular coordination to Pd(II) during the reaction. Studies on alkylidene carbene generation-C−H insertion reaction of the lactam ketones revealed that the reaction efficiency is sensitive to the reaction temperature and the amount of lithio(trimethylsilyl)diazomethane employed, which led to the development of optimal reaction conditions for effecting alkylidene carbene generation-C−H insertion. Using the optimal reaction conditions, good to high yields (53−76%) of both γ- and δ-lactam spirocycles were obtained. The synthetic utility of the spirolactams was demonstrated by the synthesis of (−)-adalinine.



INTRODUCTION

Pyrrolidines and piperidines carrying a nitrogen-substituted quaternary stereocenter are commonly found structural motifs in many natural products, as exemplified by **1**−**6** (Figure 1). In addition to this interesting structural feature, several of these natural products possess important biological activities. For example, the alkaloid salinosporamide A (marizomib, **5**) is a potent inhibitor of the 20S proteasome enzyme and is currently undergoing phase 1 clinical trial for the treatment of multiple myeloma.[1] The tricyclic alkaloid lepadiformine A (**6**) was found to show *in vitro* cytotoxicity against nasopharynx carcinoma and non-small-cell lung carcinoma.[2]

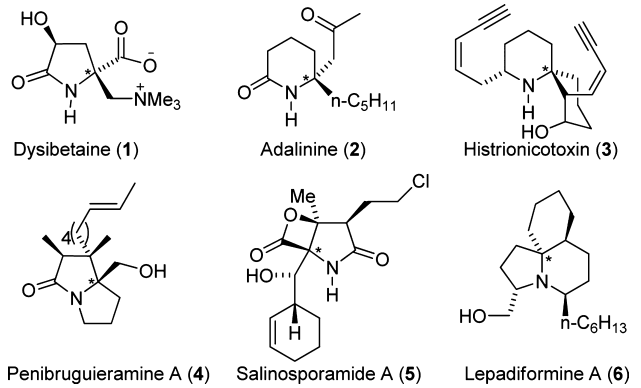


Figure 1. Representative alkaloids possessing a nitrogen-substituted quaternary stereocenter.

A wide range of synthetic methods have been developed for the construction of pyrrolidines and piperidines carrying a nitrogen-substituted quaternary center.[3] However, the majority of the studies reported are aimed at target-oriented synthesis[4] and, therefore, are not flexible for the synthesis of other structurally varied motifs. Further, a major challenge for the enantioselective syntheses of these azaheterocycles is the asymmetric creation of the nitrogen-substituted quaternary stereocenter,[5] and because of this, most of the studies[3e−g,i,4e,6] are limited to racemic syntheses. The most commonly reported methods for the enantioselective syntheses of pyrrolidines and piperidines carrying a nitrogen-substituted quaternary center include the addition of nucleophiles to iminium and *N*-acyliminium ions,[3h,7] alkylation of enolates derived from pyrrolidine- and piperidine-2-carboxylates,[8] 1,3-dipolar cycloadditions of alkenes and azomethine ylides,[9] oxidative dearomatizations,[10] and [3,3]-sigmatropic-[11] and semipinacol-type rearrangements.[12] However, among these reported approaches, limitations such as low overall efficiency,[11c] limited substrate scope,[7b,10c] and stereoselectivity issues[7a,12c] have hampered their wider synthetic applications.

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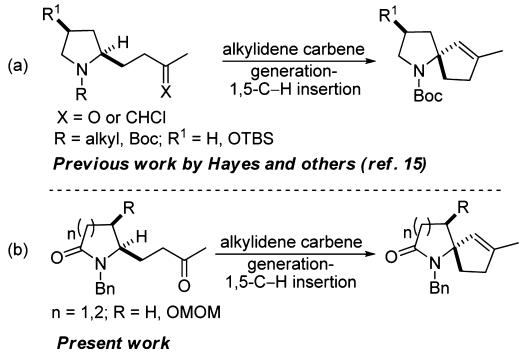
Alkylidene carbene C−H insertion reaction is an invaluable synthetic tool for the functionalization of unactivated C−H bonds.[13] This reaction usually proceeds with retention of stereochemistry at the stereodefined tertiary centers and, therefore, is very useful for the formation of quaternary centers with complete stereochemical control.[14] Previous studies[15] by Hayes and other workers have shown that the 1,5-alkylidene carbene C−H insertion reaction of pyrrolidine-based systems is an effective approach for the synthesis of spirocyclic pyrrolidine compounds (Scheme 1a). In contrast, no studies of the alkylidene carbene C−H insertion method have been applied to piperidine-based systems for the construction of spirocyclic piperidine compounds. Further, a survey of the literature also showed that alkylidene carbene C−H insertion reactions of lactams have not yet been reported. In this context, we have investigated the alkylidene carbene generation-1,5-C−H insertion of 5-(3-oxobutyl)pyrrolidin-2-ones and 6-(3-oxobutyl)piperidin-2-ones to develop a general approach for the enantioselective synthesis of spirolactams (Scheme 1b). When compared to the simple pyrrolidine-based spirocycles, the presence of a carbonyl group in the spirolactam products would provide avenues to carry out synthetic transformations on the lactam moiety and, therefore, would increase their synthetic utility. Our studies showed that the efficiency of the alkylidene carbene C−H insertion reaction in lactams is very sensitive to the reaction conditions; however, under the optimized conditions, both γ- and δ-lactams afforded the corresponding spirolactams in very good yields. The application of the developed approach was successfully demonstrated in the total synthesis of coccinellid alkaloid, (−)-adalinine (**2**, Figure 1).

Scheme 1. Alkylidene Carbene C−H Insertion Approach for Synthesis of 1-Azaspirocycles

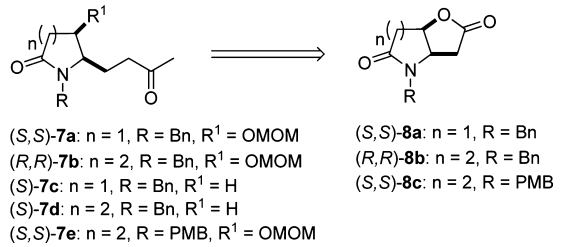


RESULTS AND DISCUSSION

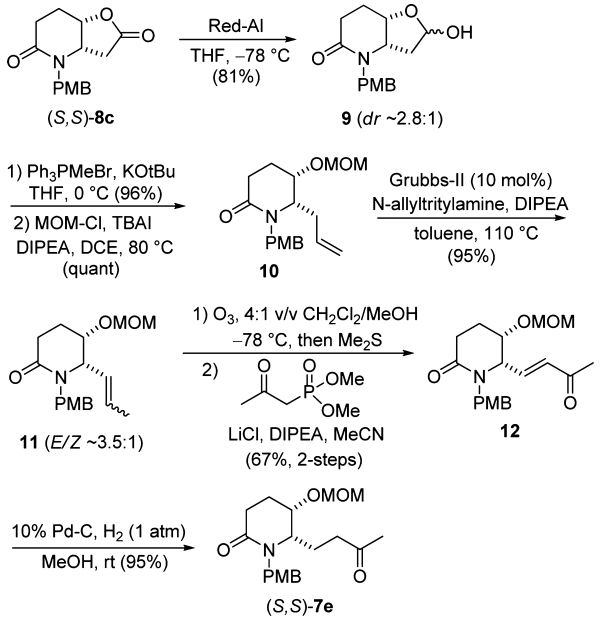
The preparation of enantiopure lactam ketones **7a−e** required for the alkylidene carbene C−H insertion studies was first investigated (Scheme 2). Compounds **7a−e** would allow us to assess (a) the influence of the N-protecting group (*N*-PMB vs *N*-Bn) and (b) the effect of C4 (or C5) substitution (OMOM vs H) on the efficiency of the alkylidene carbene C−H insertion reaction.

The lactam ketones **7a−e** were prepared from the known nonracemic bicyclic lactam lactones (BLLs) **8a−c**, which we previously reported.[16] Thus, the synthesis of *N*-PMB δ-lactam ketone (*S*,*S*)-**7e** from BLL (*S*,*S*)-**8c**[16a] (Scheme 3) was undertaken first in order to delineate a synthetic route, which would also be applicable toward the preparation of other δ-lactam ketones **7a−d**. Chemoselective reduction of the BLL-**8c** with Red-Al at −78 °C efficiently gave the bicyclic lactol **9** in 81% yield. Wittig olefination of **9** with methylidenetriphenylphosphorane (Ph_3PMeBr, KO^tBu), followed by the conversion of the resulting alkenol to the MOM-ether **10**, was achieved in 96% yield. At this stage, the isomerization of the terminal alkene in **10** to the internal alkene in **11** was effected by treating **10** with 10 mol % of Grubbs-II catalyst in the presence of *N*-allyltritylamine[17] and *N*,*N*-diisopropylethylamine in refluxing toluene to provide **11** in 95% yield as an inseparable 3.5:1 mixture of *E*/*Z* diastereomers. Ozonolysis of **11**, followed by Horner−Wordsworth−Emmons (HWE) olefination of the resulting crude aldehyde with dimethyl 2-oxopropylphosphonate gave the enone **12** in 67% yield. Catalytic hydrogenation of **12** afforded the required methyl ketone (*S*,*S*)-**7e**.

Scheme 2. Lactam Ketones 7a−e from BLLs 8a−c



Scheme 3. Preparation of δ-Lactam Ketone (*S*,*S*)-7e



Although the δ-lactam ketone **7e** was obtained in good overall yield (47%) from BLL-**8c**, this route required a lengthy seven-step sequence. To find a more expedient way for the preparation of lactam ketones **7a−d** from the respective BLLs **8a**,**b**[16b] (Scheme 4), we investigated an alternative approach that involved the Wacker oxidation of lactams carrying an internal alkene side chain typified by **13** (Scheme 4). The lactam alkenes **13** can be readily prepared from the nonracemic BLLs **8**.

The requisite internal alkenes **13a−d** were prepared according to the route shown in Scheme 5. Reduction of the BLLs **8a**,**b** to the corresponding diastereomeric lactols **14a**,**b**, followed by Wittig olefination of **14a**,**b** with ethylidenetriphe-

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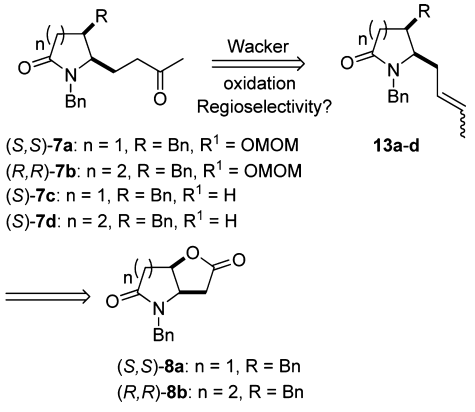
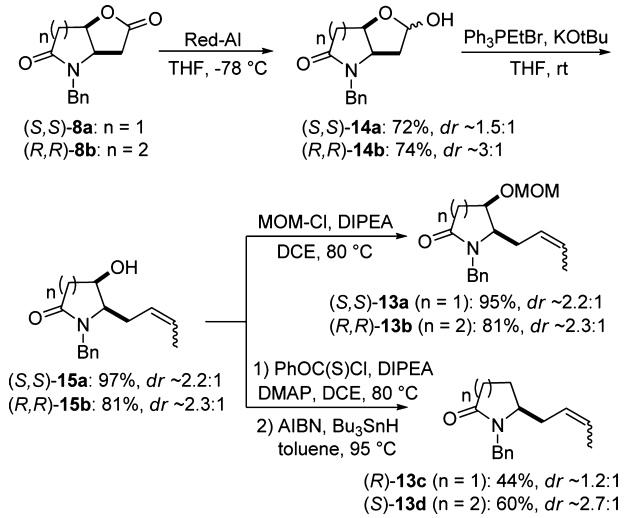
Scheme 4. Wacker Oxidation Based Approach for Synthesis of 7a−d



Scheme 5. Lactam Alkenes 13a−d from BLLs 8a,b

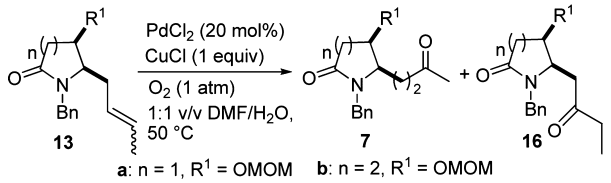


nylphosphorane (PPh_3EtBr, KO^tBu), gave the alkenols **15a,b** as inseparable mixtures of *E*/*Z* diastereomers in good yields. The stereochemistry of the double bond in **15a,b** was not determined due to extensive overlap of the olefinic proton signals in the ^1H NMR spectrum. Subsequent protection of the hydroxyl group in **15a,b** as the MOM ether afforded the lactam alkenes **13a,b**. Alcohols **15a,b** were also subjected to deoxygenation via tributyltin hydride reduction of their thiocarbonate derivatives to obtain the lactam alkenes **13c,d**.

With the lactam alkenes **13a−d** in hand, their Wacker oxidation was investigated, and the results are summarized in Table 1. Thus, treating the lactam alkenes **13a−d** under standard[18] Wacker conditions (20 mol % $PdCl_2$, 1 equiv of CuCl, O_2 (1 atm), 1:1 v/v DMF/H_2O, 50 °C) preferentially gave the desired methyl ketones **7a−d** over the regioisomeric ethyl ketones **16a−d** (entries 1−4) in very good yields (78−88%), and with excellent selectivity (≥92:8). It is useful to note that the geometry of the alkene double bond in **13a−d** had no influence on the yield and regioselectivity of the Wacker reaction (entries 1−4).

Grubbs and co-workers have recently reported[19] modified conditions (5 mol % $Pd(OAc)_2$, 1 equiv of benzoquinone, 1.4 equiv of 49% aqueous HBF_4, O_2 (1 atm), 7:1 v/v MeCN/H_2O, rt) for the regioselective Wacker oxidation of acyclic internal alkenes. Although no comparison studies were conducted

Table 1. Wacker Oxidation of Lactam Alkenes 13a−d



entry	substrate	*dr*[b]	yield[c] (%)	ratio[d] (7:16)
1	(*S*,*S*)-**13a**	2.2:1	94	92:8
2	(*R*,*R*)-**13b**	2.3:1	95	94:6
3	(*R*)-**13c**	1.2:1	83	94:6
4	(*S*)-**13d**[a]	2.7:1	94	92:8

[a]Wacker oxidation of **13d** under the conditions reported[19] by Grubbs afforded **7d** and **16d** in a ratio of 83:17, and in a combined 91% yield. [b]The stereochemistry of the double bond for the major diastereomers in **13a−d** was not determined due to the extensive overlap of olefinic proton signals in the ^1H NMR spectrum. [c]Combined yields of **7a−d** and **16a−d**. [d]Ratio based on the isolated yields of **7a−d** and **16a−d**.

between the standard Wacker and the modified conditions in their work, we decided to test these conditions on lactam olefin **13d** since they are milder and require lower loadings of Pd catalyst. However, oxidation under these conditions led to lower regioselectivity, affording **7d** and **16d** in a ratio of 83:17 compared to the 92:8 ratio observed under the standard conditions. The combined yield of **7d** and **16d** under the modified conditions was 91%.

The high regioselectivity observed in the Wacker oxidation of lactam alkenes **13a−d** is intriguing. It is reported[19,20] that the regioselectivity in Wacker oxidation of alkenes is found to be influenced by the presence of coordinating groups that are in close proximity to the double bond. For example, studies by Feringa and co-workers[20d] have shown that Wacker oxidation of allylic phthalimides selectively produced aldehydes as the major products, where coordination of the imide group with palladium was suggested as the regioselectivity controlling factor. Thus, the presence of coordinating functional groups in alkene substrates is assumed to predominately favor the oxidation at the distal site of the double bond over the proximal site. In our case, we surmise that the lactam ring might have played a role in governing the regioselectivity of the Wacker oxidation of **13a−d**, possibly involving the coordination of nitrogen to palladium; coordination of carbonyl oxygen to palladium was considered less likely for geometrical reasons.

The Wacker oxidation of alkenes **17a−d** (Table 2) was next investigated to test our hypothesis of lactam nitrogen coordination. Studies on **13d**, **17a−c** will be useful to evaluate the influence of the lactam ring on the regioselectivity in internal as well as terminal alkenes. Further, Wacker oxidation of **17d**, in which the alkene functionality is allylic to the lactam unit, is useful to test whether this substrate will behave similarly to the lactam alkenes **13a−d** (Table 1).

As mentioned above, Wacker oxidation of lactam alkene **13d** predominately favored the formation of methyl ketone **7d** over the ethyl ketone **16d** (**7d**:**16d** = 92:8). In contrast, when alkene **17a**[21] that does not possess any coordinating functional groups was subjected to Wacker oxidation, the ketones **18a**[23] and **19a** (entry 2) were obtained in a ratio of 62:38, respectively, and in a 30% combined yield. The observed regioselectivity in the reaction of **17a** is much lower when compared to that of **13d**. The Wacker oxidation of terminal alkenes **17b**[22] and **17c** was

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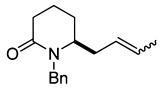
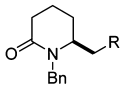
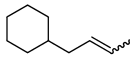
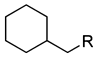
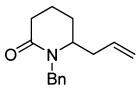
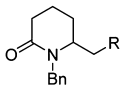
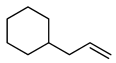
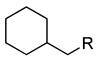
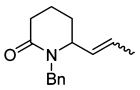
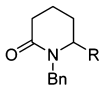
Table 2. Wacker Oxidation of Alkenes 17a−d

Entry	Substrate	Product(s)	Yield[i]	Ratio
1[a]	 **13d** (*dr* ~2.7:1)	 **7d**: R = $CH_2C(O)CH_3$ **16d**: R = $C(O)CH_2CH_3$	94	**7d**:**16d** = 92:8[j]
2	 **17a**[b] (*E*:*Z* = 1:5.5)	 **18a**[e]: R = $CH_2C(O)CH_3$ **19a**[f]: R = $C(O)CH_2CH_3$	30	**18a**:**19a** = 62:38[k]
3	 **17b**[c]	 **18b**: R = CH_2CHO **19b**[g]: R = $C(O)CH_3$	85	**18b**:**19b** = 22:78[l]
4	 **17c**	 **18c**: R = CH_2CHO **19c**[h]: R = $C(O)CH_3$	68	**18c**:**19c** = 0:100
5	 **17d**[d]	 **18d**: R = $CH_2C(O)CH_3$ **19d**: R = $C(O)CH_2CH_3$	0	no reaction

[a]Result from Table 1, entry 4, included here for comparison purposes. [b](*Z*)-**17a** has been reported[21] in the literature. [c](*R*)-**17b** has been reported[22] in the literature. [d]*E*/*Z* ratio of **17d** was not determined due to the extensive overlap of signals in the ^{1}H NMR spectrum. [e]**18a** has been reported[23] in the literature. [f]**19a** has been reported[24] in the literature. [g]**19b** has been reported[25] in the literature. [h]**19c** has been reported[26] in the literature. [i]Combined yield of regioisomeric products. [j]Ratio based on the isolated yields of **7d** and **16d**. [k]Ratio determined based on the ^{1}H NMR integration of methyl singlet at δ 2.11 (**18a**) and the methyl triplet at δ 1.02 (**19a**). [l]Ratio determined based on the ^{1}H NMR integration of benzylic methylene proton doublets at δ 5.32 (**18b**) and δ 5.00 (**19b**).

next examined to determine whether the lactam group still has any influence on regioselectivity. Wacker oxidation of the lactam alkene **17b** (entry 3) gave **18b** and **19b**[24] (**18b**:**19b** = 22:78) in 85% combined yield, whereas the alkene **17c** only resulted in the formation of **19c**[25] (entry 4) in 68% yield. Wacker oxidations of terminal alkenes are usually expected to follow Markovnikov's rule, as in the case of **17c**, to give the corresponding ketones as the predominant products. Therefore, formation of the aldehyde **18b** (19%) via anti-Markovnikov type hydration of **17b** suggests that the lactam ring also has an influence on the regioselectivity in terminal alkenes. The Wacker oxidation of **17d**, in which the alkene double bond is now allylic to the lactam unit, was examined (entry 5). It was of interest to determine whether a similar regioselectivity outcome, as was observed for the lactam olefins **13a−d** (Table 1), would result in the preferential formation of the methyl ketone **18d** over the ethyl ketone **19d**. However, none of the expected **18d** and **19d** were detected and only unreacted **17d** (90%) was recovered. The complete loss of reactivity in **17d** was unexpected and could be due to the increased steric hindrance at the alkene functionality in **17d** when compared to the lactam alkenes **13a−d**.

Overall, the results from the above studies (Table 2) provided support for our hypothesis that the regioselectivity observed in the Wacker oxidation of **13a−d** might have been influenced by the coordination of the lactam nitrogen to the palladium. Most importantly, the ability of a weak electron donor such as the lactam nitrogen to coordinate with the palladium and thereby controlling the regioselectivity in Wacker oxidation of lactam alkenes is noteworthy.

Having developed a more efficient route for the preparation of the lactam ketones **7a−e**, we turned our attention toward the alkylidene carbene generation-1,5-C−H insertion studies. We chose to use Ohira's protocol[27] for the generation of alkylidene carbenes by treatment of lactam ketones **7a−e** with lithio-trimethylsilyldiazomethane (LTDM). The reaction conditions

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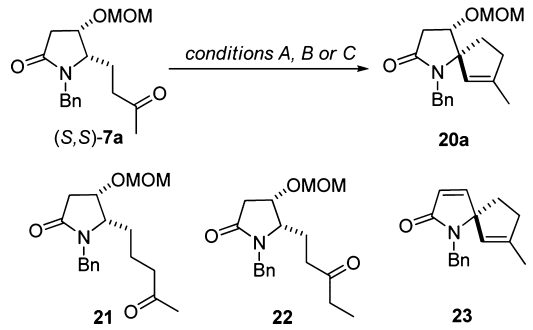
employed for the generation of alkylidene carbenes from ketones using LTDM are basic. We chose the γ-lactam ketone **7a** to develop optimal reaction conditions since it is more sensitive to basic conditions when compared to the lactam ketones **7b–e**. The basic nature of LTDM can potentially cause β-elimination in **7a** via loss of the methylene hydrogen α- to the lactam carbonyl group and the OMOM substituent and, therefore, can interfere with the generation of the alkylidene carbene.

The alkylidene carbene generation-C–H insertion of **7a** was investigated under three different reaction conditions A, B, and C, and the results are summarized in Table 3.

Table 3. Optimization of Alkylidene Carbene Generation-C–H Insertion Reaction Conditions



			isolated yield (%)			
entry	conditions[a]	LTDM (equiv)	**20a**	**21**	**22**	**23**
1	A	1.9	40	19	8	
2	B	3.0	25			
3	C	1.9	53			5

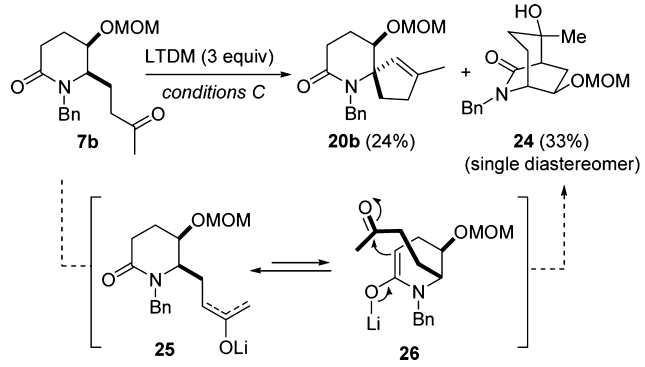
[a]Conditions A: reaction temperature was raised gradually over a period of 1 h from −78 to 0 °C after 30 min of addition of **7a**. Conditions B: reaction temperature was raised immediately from −78 to 0 °C after 20 min of addition of **7a**. Conditions C: reaction temperature was raised immediately from −78 to 0 °C after 20 min of addition of **7a**.

The *in situ* generation of the alkylidene carbene from ketone **7a** was performed under the most commonly employed reaction conditions (entry 1, conditions A) as reported in the literature.[15a,f,27] Thus, LTDM was generated by treating trimethylsilyldiazomethane (TMSDM, 2.0 equiv) with *n*-BuLi (1.9 equiv) in THF at −78 °C, followed by the addition of a THF solution of **7a** after 45 min. The resulting brown colored solution was stirred at −78 °C for 30 min, and then the reaction temperature was gradually allowed to warm to 0 °C over a period of 1 h. Under these conditions, the spirolactam **20a** was isolated in 40% yield in addition to two unexpected ketones **21** (19%) and **22** (8%). The formation of the homologated ketones such as **21** and **22** is not usually observed under LTDM reaction conditions, but is more commonly encountered in Lewis acid catalyzed reactions of carbonyl compounds with TMSDM.[28]

The effect of reaction temperature on the alkylidene carbene generation and C–H insertion was next examined by warming the reaction mixture immediately from −78 to 0 °C after 20 min of adding a THF solution of **7a** to LTDM (entry 2, conditions B). To ensure the complete consumption of ketone **17a**, an excess of LTDM (3.0 equiv) was used. However, under these conditions, the spirolactam **20a** was obtained in only 25% yield. A complex mixture of unidentified polar components was also isolated in this reaction. We reasoned that the use of excess LTDM might have led to the decomposition of **7a** via unidentified reaction pathways.

In parallel studies, we have also studied the C–H insertion of δ-lactam ketone **7b** under conditions B (Scheme 6), which led

Scheme 6. Alkylidene Carbene Generation-C–H Insertion of 7b under Conditions B



to the isolation of an unexpected bicyclic compound **24** (33%) along with the C–H insertion product **20b** (24%). This result suggests that the use of 3 equiv of LTDM under conditions B might have led to the formation of enolate **25** in competition with the generation of the alkylidene carbene. The enolate **25** is expected to be in equilibrium with **26**, in which intramolecular nucleophilic addition of the α-carbanion to the keto group explains the formation of bicycle **24**.

On the basis of the above results, we then investigated the use of 1.9 equiv of LTDM and warming the reaction mixture immediately to 0 °C after 20 min (conditions C). Under these conditions, the spirolactam **20a** was obtained in an improved 53% yield. A minor quantity of **23** (5%) was also isolated in this reaction, which had likely resulted from base-mediated β-elimination of the MOM group from the spirolactam **20a**. None of the rearrangement products that were observed under conditions A were detected.

Overall, conditions C provided the best results compared to the conditions A and B that were tested for formation of the spirolactam **20a**. In comparison to the yields (53–65%) obtained in the pyrrolidine-based substrates reported[15a–d] by Hayes and co-workers, and in spite of the base sensitivity of the lactam ketone **7a**, the yield obtained for **20a** is comparable and synthetically useful.

To further determine the scope of the reaction, structurally varied γ- and δ-lactam ketones **7b–e** were subjected to alkylidene carbene generation-tertiary C–H insertion under the optimized reaction conditions C, and the results are shown in Table 4.

The alkylidene carbene generation-C–H insertion of lactam ketones **7b–e** (entries 1–4) under conditions C gave the corresponding spirolactams **20b–e** in good yields. A comparison of the yields observed in the formation of **20b** (72%) and **20e** (55%) indicates that the *N*-benzyl protecting group is conducive toward more efficient alkylidene carbene generation-C–H insertion than the *N*-(*p*-methoxybenzyl) group.[29] Further, the large improvement in the yield of **20c** compared to **20a** (53%, entry 3, Table 3) is likely due to the absence of a competing β-elimination pathway in lactam ketone **7c**. Importantly, generation of alkylidene carbene from lactam ketones **7b–e** led to the exclusive[30] formation of 1,5-C–H

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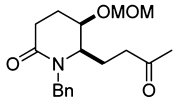
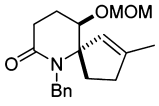
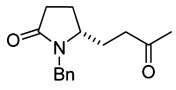
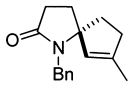
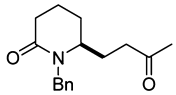
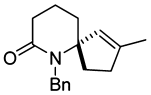
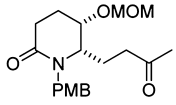
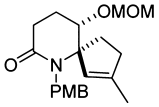
Table 4. Alkylidene Carbene Generation-C−H Insertion of 7b−e

Entry	Substrate	Product	Yield[a]
1	 **7b**	 **20b**	72
2	 **7c**	 **20c**	76
3	 **7d**	 **20d**	62
4	 **7e**	 **20e**	55

[a]Isolated yield.

insertion products, and none of the alkyne products which could have arisen from competing Fritsch−Buttenberg−Wiechell rearrangement[31] were observed. Overall, the alkylidene carbene generation-C−H insertion of lactam ketones **7a−e** was found to be successful for the formation of synthetically very useful spirolactams **20a−e**.

Having developed an efficient approach for the enantioselective synthesis of spirolactams, the synthesis of the coccinellid alkaloid (−)-adalinine (**2**) was undertaken. Adalinine was isolated[32] as a minor component from the European two-spotted ladybird beetle *Adalia bipunctata* along with the major alkaloid (−)-adaline (**27**, Figure 2). The ladybird beetle exhibits

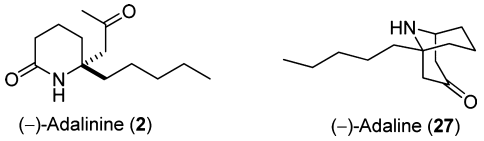
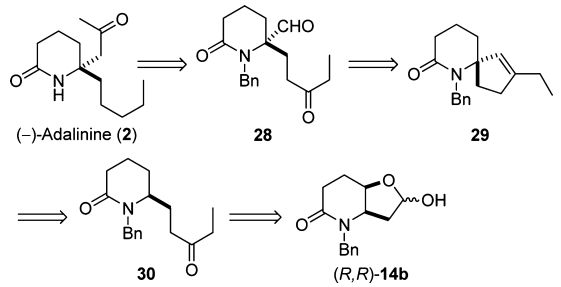


Figure 2. Alkaloids (−)-adalinine and (−)-adaline.

a defense mechanism known as reflex bleeding against predators by emitting droplets of these alkaloids. Biosynthetic studies[33] of (−)-adalinine have suggested that it is derived from (−)-adaline involving a retro-Mannich reaction. The key structural feature of adalinine is the presence of a nitrogen-bearing quaternary stereocenter, which has attracted the attention of synthetic chemists, and to date, three racemic[34] and three enantioselective[35] syntheses have been reported.

Our retrosynthetic plan for (−)-adalinine starting from the bicyclic lactam lactol (*R,R*)-**14b** (Scheme 5) is shown in Scheme 7. Adalinine can be obtained from the keto-aldehyde

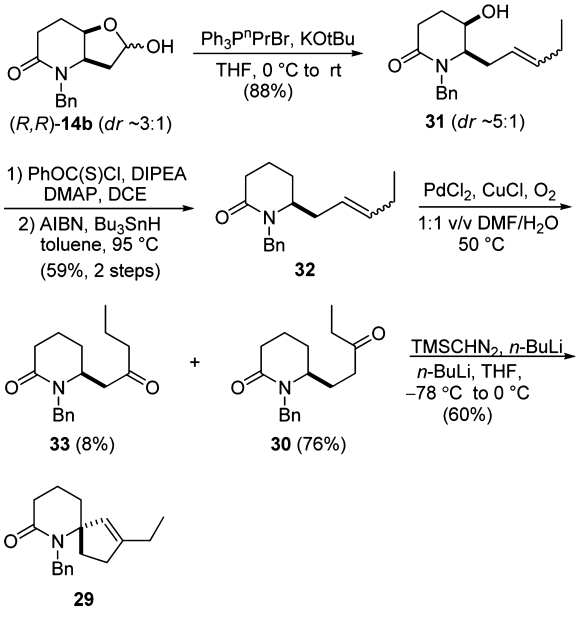
Scheme 7. Retrosynthetic Plan for (−)-Adalinine



28 in a few steps. Oxidative cleavage of the alkene in spirolactam **29** will provide the keto-aldehyde **28**. The alkylidene carbene C−H insertion reaction of the δ-lactam ethyl ketone **30** is expected to provide the spirolactam intermediate **29**. The ketone **30** can be prepared from (*R,R*)-**14b** following a similar route described for the preparation of methyl ketone (*S*)-**7d** [(*R,R*)-**14b** → (*S*)-**7d**; Scheme 5 and Table 1].

The synthesis of (−)-adalinine began with the conversion of the lactol (*R,R*)-**14b** to the alkene **31** (Scheme 8). Thus, Wittig

Scheme 8. Preparation of Spirolactam 29



olefination of (*R,R*)-**14b** with propylidenetriphenylphosphorane ($PPh_3{}^nPrBr$, KO^tBu) gave **31** as an inseparable mixture of *E*/*Z* diastereomers (~5:1) and in 88% yield. Deoxygenation of the hydroxyl group in **31** via tributyltin hydride reduction of its corresponding thiocarbonate afforded **32**. Wacker oxidation of **32** gave the ketone **30** as the major product over **33** with good regioselectivity (~91:9), which is in accordance with the selectivity observed for the oxidation of alkenes **13a−d** (Table 1). At this stage, the alkylidene carbene C−H insertion of the lactam ketone **30** was carried out under the optimized reaction

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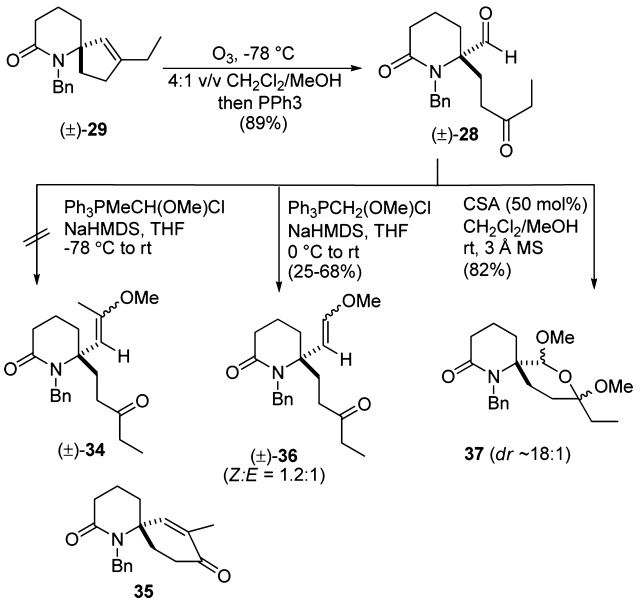
conditions (conditions C, Table 3) to form the spirolactam **29** in 60% yield. We also determined the enantiopurity of **29** by HPLC on a chiral stationary phase (Chiralpak AD column; 95:5 v/v hexane/*i*-PrOH; flow rate, 1.0 mL/min; t_R = 11.9 min for (*R*)-**29**, and t_R = 13.1 min for (*S*)-**29**), which was found to be 99% *ee*.[36] This result confirmed that the alkylidene carbene C−H insertion also proceeded with retention of the configuration in the lactam ketones.

At this juncture, the retrosynthetic plan (Scheme 7) entailed the formation of keto-aldehyde **28**, from which the side chains of adalinine can be installed. It was reasoned that the difference in reactivity between the aldehyde and ketone groups in **28** should facilitate chemoselective transformation of the aldehyde functionality. Exploratory studies on the chemoselective Wittig olefination of the aldehyde moiety were conducted using (±)-**28**. Thus, ozonolysis of (±)-**29**[36] in 4:1 v/v CH_2Cl_2/MeOH at −78 °C, followed by reduction of the ozonide with triphenylphosphine, gave the compound (±)-**28** in 89% yield (Scheme 9). Reaction of (±)-**28** with (α-methoxyethylidene)-

Scheme 9. Exploratory Chemoselective Transformations of (±)-28

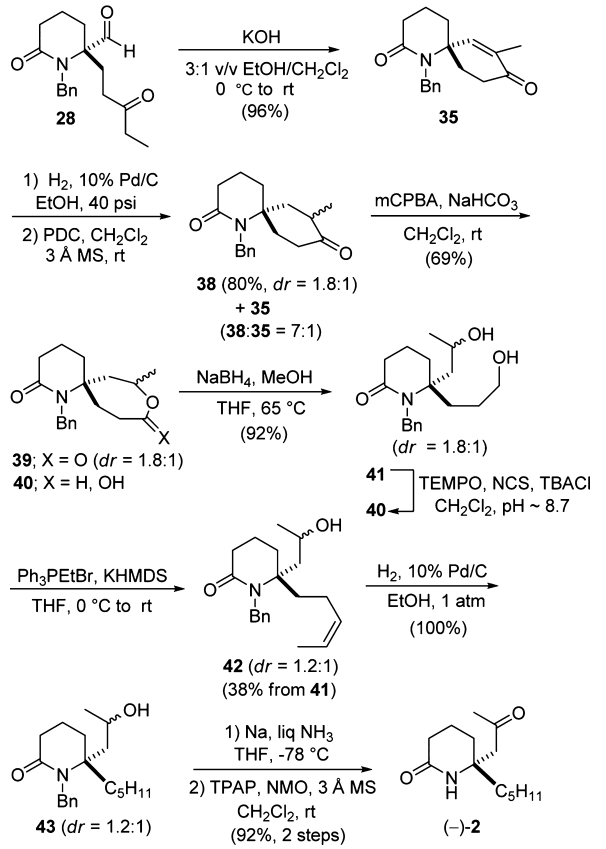


triphenylphosphorane[37] ($PPh_3MeCH(OMe)Cl$, NaHMDS) did not give the expected enol ether **34**, but instead led to the unexpected formation of the intramolecular aldol condensation product (±)-**35**[38] in 45% yield (Scheme 9). The Wittig olefination of (±)-**28** with (methoxymethylene)-triphenylphosphorane ($PPh_3CH_2(OMe)Cl$, NaHMDS) on the other hand led to the enol ether **36**. However, the yield of **36** (25−68%) was found to vary widely depending on the reaction scale and the reaction was capricious. In cases where the yield of **36** was very low, formation of side products from double Wittig olefination of both aldehyde and ketone carbonyl groups and/or intramolecular aldol reaction/condensation products were observed. Attempts to improve the yields of the Wittig reaction products by carefully optimizing reaction conditions such as by using different bases, reaction temperature, concentration of the phosphorane, or the mode of addition of phosphorane were in vain.

It is evident from the above studies that the intramolecular aldol reaction/condensation is competitive with Wittig olefination in the keto-aldehyde **28**. To circumvent this undesired competing reaction and to promote Wittig olefination at the aldehyde group, we planned to chemoselectively protect the aldehyde group in **28**, deoxygenate the keto unit, and then unmask the aldehyde function. Thus, the keto-aldehyde (±)-**28** was subjected to the acid-mediated acetalization using camphor sulfonic acid (50 mol %) in 1:1 v/v CH_2Cl_2/MeOH to form the corresponding dimethyl acetal derivative (Scheme 9). Surprisingly, the only compound isolated in 82% yield was the cyclization product **37**. Compound **37** was obtained as a mixture of two diastereomers in an approximately 18:1 ratio. The conversion of **28** to **37** was complete within 10 min, suggesting that the cyclization is instantaneous.

Informed by our studies on the attempted chemoselective transformation of (±)-**28**, an alternative approach for the conversion of **28** to adalinine was sought (Scheme 10).

Scheme 10. Conversion of Keto-aldehyde (*S*)-28 to Adalinine



Accordingly, (*S*)-**28**, prepared from (*S*)-**29** via ozonolysis, was treated with KOH (3 equiv) in 3:1 v/v EtOH/CH_2Cl_2 to effect intramolecular aldol condensation to obtain the spirocyclic enone **35** in excellent yield (96%). Catalytic hydrogenation (40 psi H_2, Parr) of **35** in the presence of 10% Pd-C (10 mol %) in ethanol gave an inseparable mixture of the ketone **38** along with minor amounts of the allylic alcohols derived from reduction of the ketone moiety and secondary alcohols formed from reduction of both the alkene and the ketone units. The hydrogenation of the enone **35** was also conducted in EtOAc to test whether the formation of alcohols can be suppressed; however, the reduction of **35** was found to be impractically

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slow. Further, attempted reduction of **35** with NaHSe[39] (generated *in situ* from selenium and $NaBH_4$ in EtOH) only led to the recovery of the unreacted starting material. The over reduction of similar lactam enones to the lactam alcohols has been previously observed in the studies[34a] of Wardrop and co-workers.

Since our attempts to suppress the formation of alcohols were not successful, the crude mixture obtained from the hydrogenation step was directly subjected to PDC oxidation. This gave an inseparable mixture of the desired lactam ketone **38** (*dr* ∼ 1.8:1) and the starting enone **35** in a 7:1 ratio. The overall yield of **38** is approximately 80% (determined based on the integration of the methyl doublets in **38** at δ 0.89 and δ 0.95, and the methyl singlet in **35** at δ 1.69 in the ^{1}H NMR spectrum), over two steps.

Baeyer−Villiger oxidation of the 7:1 mixture of **38** and **35** with mCPBA in the presence of $NaHCO_3$ in CH_2Cl_2 gave the pure lactone **39** in 69% yield (55% yield from **35**, over three steps). The lactone **39** was obtained as an inseparable mixture of diastereomers in a 1.8:1 ratio. The enone **35** was also found to react under the oxidation conditions; however, no attempt was made to isolate the resulting products. Chemoselective reduction of the lactone **39** to form the lactol **40** by treating with DIBAL-H in CH_2Cl_2 at −78 °C gave a complex mixture of products, which made isolation difficult. Therefore, the crude product was directly subjected to Wittig olefination in the next step without any purification. Treating the crude lactol **40** with ethylidenetriphenylphophorane (PPh_3EtBr, KHMDS) afforded the olefin **42** (*dr* ∼ 1:1) in 25% yield over two steps. In order to optimize the selective conversion of lactone **39** to lactol **40** and to improve the overall yield of **42**, the use of other reducing reagents such as Red-Al and $NaAlH(OEt)(OCH_2CH_2OCH_3)_2$[40] (generated *in situ* from Red-Al and EtOH in THF) was investigated. However, reduction of **39** with these reagents also resulted in formation of a complex mixture of products.

Because of the problems encountered in the direct conversion of **39** to **40**, a two-step procedure involving a reduction−oxidation sequence was investigated for this transformation. The lactone **39** was cleanly reduced[41] to the diol **41** with $NaBH_4$ (2.5 equiv) in THF/MeOH at 65 °C in excellent yield. Treating[42] **41** with catalytic amounts of TEMPO (20 mol %) in the presence of *N*-chlorosuccinimide (1.5 equiv) and tetrabutylammonium chloride (15 mol %) under biphasic conditions gave the lactol **40**. The lactol **40** was obtained as an inseparable mixture together with small amounts of the regenerated lactone **39**. The unreacted diol **41** (33%) was also recovered and recycled. Wittig olefination of the mixture of **40** and **39** in the next step gave the alkenol **42**. The yield of alkenol **42** is 38%, over two steps from **41**. The lactone **39** did not react under the Wittig reaction conditions and was recovered.

The alkenol **42** was converted to adalinine in three steps. Thus, catalytic hydrogenation (1 atm H_2, balloon) of **42** over 10% Pd-C (10 mol %) in EtOH gave **43** in quantitative yield. *N*-Debenzylation of **43** under Birch reduction conditions, followed by the oxidation[35c] of the corresponding alcohol using TPAP and NMO, gave (−)-adalinine (**2**) in 92% yield. The ^{1}H and ^{13}C NMR spectral data and $[\alpha]_D^{23}$ −29.8 (*c* 0.61, CH_2Cl_2) {lit.[35c] $[\alpha]_D^{20}$ −28.3 (*c* 1.6, CH_2Cl_2); lit.[35b] $[\alpha]_D^{20}$ −30.4 (*c* 0.8, CH_2Cl_2)} of (−)-**2** are in good agreement with those reported in the literature. Further, the enantiopurity of (−)-adalinine was confirmed by HPLC on a chiral stationary phase (Chiralcel OD; hexane/*i*-PrOH (90:10, v/v); flow rate, 1.0 mL/min; t_R = 10.9 min for (*S*)-**2** and t_R = 12.1 min for (*R*)-**2**), which was found to be >99% *ee*.[43]

CONCLUSIONS

An alkylidene carbene generation-1,5-C−H insertion reaction of 5-(3-oxobutyl)pyrrolidin-2-ones and 6-(3-oxobutyl)-piperidin-2-ones was successfully developed for the enantioselective formation of 7-methyl-1-azaspiro[4,4]non-6-ene-2-ones and 2-methyl-6-azaspiro[4,5]dec-1-ene-7-ones, respectively. The enantiopure γ- and δ-lactam ketones **7a−e** required for the alkylidene carbene C−H insertion reaction studies were prepared from the corresponding chiral nonracemic bicyclic lactam lactones **8a−c**. Among the two different routes that were investigated for the synthesis of lactam ketones, the route based on the Wacker oxidation of internal alkenes **13a−d** was found to be useful where high regioselectivity was realized. Further studies on Wacker oxidation strongly suggested that the lactam nitrogen may have played a role in influencing the regioselectivity via internal coordination to palladium.

Careful studies to delineate reaction conditions for the alkylidene carbene generation-C−H insertion revealed that the efficiency of the C−H insertion reaction is sensitive to the reaction temperature and the amount of lithiotrimethylsilyldiazomethane employed. These studies led to the development of optimized reaction conditions for alkylidene carbene generation-C−H insertion that is applicable to both γ- and δ-lactam ketones. Under the optimized conditions, synthetically useful yields of spirolactams were obtained. When compared to the pyrrolidine-based spirocycles reported by other workers,[15] the spirolactams prepared in our study are more functionalized; the presence of carbonyl and the OMOM groups in the lactam ring would provide avenues for further synthetic transformations. In our studies, the synthetic utility of the spirolactams was demonstrated by the successful conversion of spirolactam **29** to (−)-adalinine. Although the overall yield obtained for (−)-adalinine is low (2.5% from (*R*,*R*)-**8b**, 17 steps) compared to the previously reported syntheses,[35] the utility of our nonracemic spirolactams as intermediates in synthesis is clearly demonstrated.

EXPERIMENTAL SECTION

General. IR spectra were recorded using either neat oil or film (CH_2Cl_2) on NaCl plates, and only the diagnostic absorptions were reported. ^{1}H (300 or 500 MHz) and ^{13}C{^{1}H} (75 or 125 MHz) NMR spectra were recorded in $CDCl_3$ unless stated otherwise. The residual $CHCl_3$ singlet at δ_H = 7.26 and the $CDCl_3$ triplet centered at δ_C = 77.0 were used as internal references for ^{1}H and ^{13}C NMR spectra, respectively. High-resolution mass spectra in electron impact (EI) and chemical ionization (CI) modes were recorded on a double focusing sector field mass spectrometer, in the field desorption (FD) mode using a time-of-flight mass spectrometer, and in the electrospray ionization (ESI) mode using a quadrupole time-of-flight mass spectrometer. Optical rotations were recorded at the Na_D line. Reaction progress was monitored by thin-layer chromatography on silica gel 60_{F254} precoated (0.25 mm) on aluminum-backed sheets. Air- and moisture-sensitive reactions were conducted under a static pressure of argon. All organic extracts were dried over anhydrous Na_2SO_4. Chromatographic purification implies flash column chromatography, which was performed on silica gel 60 Å (230−400 mesh). Dichloromethane, DMF, toluene, chloroform, methanol, and acetonitrile were dried by distillation from calcium hydride. THF and diethyl ether were dried by distillation from sodium using sodium benzophenone ketyl as indicator. Ethanol was dried by distillation from $Mg(OEt)_2$. The preparation of bicyclic lactam lactones (*S*,*S*)-

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8a,[16b] (*R*,*R*)-**8b**,[16b] (*S*,*S*)-**8c**,[16a] and the allyl δ-lactam **10**[16a] were previously reported.

(5*S*,6*S*)-1-(*p*-Methoxybenzyl)-5-(methoxymethoxy)-6-(prop-1-enyl)piperidin-2-one (11). To the allyl δ-lactam **10** (134 mg, 0.42 mmol) in toluene (8 mL) under argon at rt were sequentially added allyltrityl amine (251 mg, 0.84 mmol), Grubbs-II catalyst (36 mg, 0.04 mmol), and DIPEA (0.07 mL, 0.42 mmol). The resulting wine red color solution was then allowed to heat at reflux for 6 h, during which time the color of the solution was changed to dark brown. Toluene was evaporated under reduced pressure, and the crude product was purified by chromatography (2:1 petroleum ether/EtOAc, then 1:1 petroleum ether/EtOAc) to give an inseparable *E*/*Z* mixture of **11** (127 mg, 95%) as a colorless oil: $[\alpha]_D^{22}$ +96.0 (*c* 0.67, $CHCl_3$); IR (CH_2Cl_2) 3047, 2947, 2838, 1639, 1513 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (*E*-**11**) 7.07−7.15 (m, 2 H), 6.76−6.84 (m, 2 H), 5.34−5.63 (m, 2 H), 5.30 (d, *J* = 14.6 Hz, 1 H), 4.58 (d, *J* = 6.9 Hz, 1 H), 4.55 (d, *J* = 6.9 Hz, 1 H), 3.72−3.88 (m, 2 H), 3.75 (s, 3 H), 3.64 (d, *J* = 14.6 Hz, 1 H), 3.27 (s, 3 H), 2.37−2.71 (m, 2 H), 1.78−2.04 (m, 2 H), 1.75 (d, *J* = 5.6 Hz, 1 H); δ (discernible signals for *Z*-**11**) 5.74−5.86 (m, 1 H), 5.32 (d, *J* = 14.6 Hz, 1 H), 4.16 (dd, *J* = 9.9, 4.8 Hz, 1 H), 3.62 (d, *J* = 14.6 Hz), 3.28 (s, 3 H), 1.53 (dd, *J* = 7.0, 1.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (*E*-**11**) 169.1, 158.7, 130.0, 129.2, 126.2, 113.8, 95.2, 72.9, 59.9, 55.5, 55.1, 46.8, 29.1, 23.4, 17.8 (discernible signals for *Z*-**11**) 169.1, 129.6, 129.3, 126.3, 95.1, 72.2, 54.5, 46.2, 29.0, 23.9, 13.2; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{25}NO_4$ 319.17836; Found 319.17841.

The ratio of the (*E*)- and (*Z*)-**11** was ∼3.5:1, respectively, based on integration of the methyl signals at δ 1.75 and δ 1.53 in the ^1H NMR spectrum.

(5*S*,6*S*)-1-(*p*-Methoxybenzyl)-5-(methoxymethoxy)-6-((*E*)-3-oxobut-1-enyl)piperidin-2-one (12). An ozone-oxygen stream was bubbled into a solution of **11** (137 mg, 0.43 mmol) in 4:1 v/v CH_2Cl_2 and MeOH (10 mL) at −78 °C for 15 s, at which time a pale blue color remained in the solution and TLC analysis showed complete conversion of the starting material. This solution was purged with argon, and Me_2S (1.9 mL, 25.8 mmol) was added at −78 °C. The reaction mixture was stirred for 2 h at −78 °C, followed by 30 min at rt. The solvent was removed under reduced pressure, and the crude aldehyde was dried under high vacuum over P_2O_5. The aldehyde was dissolved in MeCN (2 mL) and was stored over molecular sieves prior to use in the next step.

To powdered LiCl (22 mg, 0.51 mmol) in MeCN (6 mL) under argon at rt was added dimethyl 2-oxopropylphosphonate (0.07 mL, 0.51 mmol), and the resulting suspension was stirred for 15 min. *N*,*N*-Diisopropylethylamine (0.07 mL, 0.43 mmol) was added, and the mixture was stirred for another 30 min, resulting in a clear colorless solution. To this solution at 0 °C was then added the above aldehyde in MeCN (2 mL) through cannula. The reaction mixture was stirred at 0 °C for 30 min and at rt, overnight. Saturated aqueous NH_4Cl was added at 0 °C, and MeCN was evaporated under reduced pressure. The crude residue was diluted with CH_2Cl_2 (10 mL) and washed once with brine. Excess solid NaCl was added to the aqueous layer, and the aqueous phase was back-extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (1:2 petroleum ether/EtOAc, then 1:3 petroleum ether/EtOAc) to afford **12** (99 mg, 67% over two steps) as a colorless oil: $[\alpha]_D^{22}$ −90.2 (*c* 0.61, $CHCl_3$); IR (CH_2Cl_2) 2997, 2835, 2950, 2900, 1698, 1678, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.04−7.12 (m, 2 H), 6.75−6.83 (m, 2 H), 6.73 (dd, *J* = 16.2, 5.7 Hz, 1 H), 6.06 (dd, *J* = 16.2 Hz, 1 H), 5.25 (d, *J* = 14.7 Hz, 1 H), 4.58 (d, *J* = 6.9 Hz, 1 H), 4.54 (d, *J* = 6.9 Hz, 1 H), 4.10 (dd, *J* = 5.4, 5.4 Hz, 1 H), 3.85 (ddd, *J* = 10.2, 5.4, 5.4 Hz, 1 H), 3.73 (s, 3 H), 3.63 (d, *J* = 14.7 Hz, 1 H), 3.25 (s, 3 H), 2.59 (ddd, *J* = 18.1, 7.0, 3.9 Hz, 1 H), 2.46 (ddd, *J* = 18.1, 9.4, 7.7 Hz, 1 H), 2.22 (s, 3 H), 1.74−1.97 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.2, 168.9, 159.0, 142.3, 132.9, 129.3, 128.6, 113.9, 95.4, 73.0, 59.4, 55.6, 55.1, 47.8, 28.9, 27.4, 23.7; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{19}H_{25}NO_5$ 347.1733; Found 347.1739.

(5*S*,6*S*)-1-(*p*-Methoxybenzyl)-5-(methoxymethoxy)-6-(3-oxobutyl)piperidin-2-one (7e). The enone **12** (78 mg, 0.22 mmol) was dissolved in MeOH (6 mL), and hydrogenated (1 atm, balloon) over 10% palladium on carbon (8 mg). After 2.5 h at rt, the solution was filtered through a pad of Celite, and MeOH was evaporated under reduced pressure. The crude product was purified by chromatography (EtOAc) to give the ketone (*S*,*S*)-**7e** (74.5 mg, 95%) as a colorless oil: $[\alpha]_D^{23}$ −60.2 (*c* 0.95, $CHCl_3$); IR (CH_2Cl_2) 3054, 2954, 2838, 1713, 1639, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.13−7.21 (m, 2 H), 6.79−6.86 (m, 2 H), 5.27 (d, *J* = 14.8 Hz, 1 H), 4.55 (d, *J* = 6.6 Hz, 1 H), 4.51 (d, *J* = 6.6 Hz, 1 H), 3.86 (d, *J* = 14.8 Hz, 1 H), 3.70−3.80 (m, 4 H), 3.38 (ddd, *J* = 7.4, 4.7, 4.7 Hz, 1 H), 3.26 (s, 3 H), 2.40−2.67 (m, 4 H), 2.10 (s, 3 H), 1.82−2.09 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.7, 169.1, 158.8, 129.2 (2 × ^{13}C), 113.8, 73.2, 56.5, 55.4, 55.1, 47.9, 40.3, 29.8, 28.6, 23.1, 22.6; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{19}H_{27}NO_5$ 349.1889; Found 349.1881.

(3a*S*,6a*S*)-4-Benzyl-hexahydro-2-hydroxyfuro[3,2-*b*]pyrrol-5-one (14a). A stock solution of 0.15 M Red-Al in toluene was made by diluting Red-Al (1.0 mL, 65% w/w in toluene) with toluene (20 mL). To a solution of Red-Al (9.0 mL, 1.35 mmol, 0.15 M) at −78 °C was added, under Ar, THF (1 mL), followed by a solution of the known[16b] (*S*,*S*)-**8a** (440 mg, 1.9 mmol) in THF (15 mL) via syringe pump (rate of addition ∼ 4 mL/min; the flask that held the solution of **8a** and the syringe were rinsed with another 3.5 mL of THF). The reaction mixture was stirred at −78 °C for 1 h, then quenched with a few drops of MeOH, followed by saturated aqueous NH_4Cl (2 mL) and allowed to warm to rt. All the volatiles were evaporated under reduced pressure; the remaining residue was diluted with CH_2Cl_2 (20 mL), and filtered through a pad of Celite. The two layers were separated, and the organic layer was washed once with brine. The aqueous layer was saturated with solid NaCl and back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (1:3 petroleum ether/EtOAc, then EtOAc, followed by 10:1 EtOAc/MeOH) afforded the lactol (*S*,*S*)-**14a** (321 mg, 72%, 86% brsm) as an off-white solid. The over-reduced diol (27 mg, 6%) and starting (*S*,*S*)-**8a** (69 mg, 16%) were also isolated. (*S*,*S*)-***14a***: mp 125−126 °C; $[\alpha]_D^{23}$ −127.7 (*c* 0.9, $CHCl_3$); IR (CH_2Cl_2) 3520−3220, 3055, 2987, 1687, 1423 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.16−7.38 (m, 5 H), 5.52−5.62 (m, 1 H), 4.91 (d, *J* = 14.8 Hz, 1 H), 4.65−4.79 (m, 1 H), 4.10 (ddd, *J* = 5.5, 5.5, 5.5 Hz, 1 H), 3.95 (d, *J* = 14.8 Hz, 1 H), 3.56−3.66 (br m, 1 H), 2.51−2.84 (m, 2 H), 1.97−2.09 (m, 2 H); δ (discernible signals for minor diastereomer) 5.13 (d, *J* = 15.0 Hz, 1 H), 4.03 (dd, *J* = 6.3, 6.3 Hz, 1 H), 3.92 (d, *J* = 15.0 Hz, 1 H), 3.44−3.55 (br m, 1 H), 2.28 (d, *J* = 14.1 Hz, 1 H), 1.77−1.90 (m, 1 H); ^{13}C NMR (CDCl3, 75 MHz) δ (major diastereomer) 172.6, 135.8, 128.7, 128.3, 127.8, 98.6, 73.7, 61.1, 44.7, 38.3, 37.6; δ (minor diastereomer) 173.1, 128.3, 127.7, 99.0, 75.8, 61.0, 44.7, 40.1, 36.3. HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{13}H_{15}NO_3$ 233.1052; Found 233.1045.

The diastereomeric ratio of (*S*,*S*)-**14a** was ∼1.5:1, based on integration of the benzylic methylene protons at δ 5.13 and δ 4.91 in the ^1H NMR spectrum.

(3a*R*,7a*R*)-4-Benzyl-hexahydro-2-hydroxyfuro[3,2-*b*]pyridin-5(6*H*)-one (14b). The lactol (*R*,*R*)-**14b** was prepared from the known[16b] bicyclic lactam lactone (*R*,*R*)-**8b** (533 mg, 2.17 mmol) according to the procedure described for the preparation of (*S*,*S*)-**14a**. Purification by chromatography (1:3 petroleum ether/EtOAc, then EtOAc) afforded the lactol (*R*,*R*)-**14b** (394 mg, 74%, 81% brsm) as a colorless oil. The starting (*R*,*R*)-**8b** (48 mg, 9%) was also recovered. (*R*,*R*)-***14b***: $[\alpha]_D^{21}$ −44.1 (*c* 0.75, $CHCl_3$); IR (neat) 3559−3110, 2933, 1628 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.18−7.36 (m, 5 H), 5.55 (d, *J* = 4.6 Hz, 1 H), 5.25−5.32 (br m, 1 H), 5.13 (d, *J* = 14.9 Hz, 1 H), 4.47 (ddd, *J* = 6.4, 2.8, 2.8 Hz, 1 H), 4.00−4.10 (m, 1 H), 4.01 (d, *J* = 14.9 Hz, 1 H), 2.30−2.52 (m, 2 H), 2.22 (ddd, *J* = 13.4, 7.9, 1.1 Hz, 1 H), 1.97−2.13 (m, 1 H), 1.71−1.87 (m, 2 H); δ (discernible signals for minor diastereomer) 5.46−5.51 (m, 1 H), 5.40 (d, *J* = 15.1 Hz, 1 H), 5.17−5.23 (br s, 1 H), 4.26−4.33 (m, 1 H), 3.76 (ddd, *J* = 6.1, 6.1, 4.0 Hz, 1 H), 2.78 (ddd, *J* = 17.2, 12.9, 4.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 171.1, 136.5, 128.4, 127.8, 127.3, 96.6, 72.0, 57.4, 47.9, 41.4, 27.2, 24.5; δ

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(minor diastereomer) 171.0, 136.4, 128.4, 127.7, 127.2, 97.3, 74.7, 57.3, 47.0, 38.8, 26.9, 24.2. HRMS (FD-TOF) m/z: $[M]^+$ Calcd for $C_{14}H_{17}NO_3$ 247.1208; Found 247.1200.

The diastereomeric ratio of (*R*,*R*)-**14b** was ~3:1, based on integration of the benzylic methylene proton signals at δ 5.13 and δ 5.40 in the ^{1}H NMR spectrum.

(4*S*,5*S*)-1-Benzyl-5-(but-2-enyl)-4-(methoxymethoxy)-pyrrolidin-2-one (13a). $Ph_3P^+EtBr^-$ (2.25 g, 6.3 mmol) was dried under vacuum at 110 °C for 1 h and cooled to rt. The above salt was suspended in THF (15 mL), and it was cooled to 0 °C under argon. KO^{t}Bu (744 mg, 6.3 mmol) was added in one portion, to the above suspension. A bright yellow suspension resulted. After 45 min at 0 °C, a solution of the lactol (*S*,*S*)-**14a** (245 mg, 1.05 mmol) in THF (8 mL) was added via cannula, and the mixture was stirred for 1 h. Saturated aqueous NH_4Cl (5 mL) was added, and the THF was evaporated off under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (1:4 petroleum ether/EtOAc) afforded the alkenol (*S*,*S*)-**15a** (249 mg, 97%) together with triphenylphosphine oxide as an inseparable mixture. The alkenol was obtained as a mixture of *Z*- and *E*-diastereomers.

(4S,5S)-1-Benzyl-5-(but-2-enyl)-4-hydroxypyrrolidin-2-one (15a). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.10−7.27 (m, 5 H), 5.30−5.51 (m, 2 H), 5.00 (d, J = 15.5 Hz, 1 H), 4.79−4.89 (br s, 1 H), 4.23−4.35 (m, 1 H), 3.90 (d, J = 15.5 Hz, 1 H), 3.29−3.40 (m, 1 H), 2.30−2.58 (m, 4 H), 1.45 (d, J = 6.05 Hz, 3 H); δ (discernible signals for minor diastereomer) 4.94 (d, J = 15.2 Hz, 1 H), 3.92 (d, J = 15.2 Hz, 1 H), 1.54 (d, J = 4.3 Hz, 3 H). The ratio of *Z*- and *E*-alkenols was found to be ~2.2:1, based on integration of the methyl doublets at δ 1.45 and δ 1.54 in the ^{1}H NMR spectrum.

To the above alkenol (*S*,*S*)-**15a** (87 mg, 0.35 mmol) in DCE (4 mL) under Ar at rt were added tetrabutylammonium iodide (2 mg, 1.5 mol %), *N*,*N*-diisopropylethylamine (0.37 mL, 2.1 mmol), and MOM-Cl (80 μL, 1.05 mmol) successively, and the resulting solution was allowed to reflux, overnight. The reaction mixture was cooled to 0 °C and diluted with CH_2Cl_2 (5 mL), and saturated aqueous Na_2CO_3 (2 mL) was added. After stirring the mixture for 15 min at the same temperature, the biphasic solution was transferred into a separatory funnel. The two layers were separated, and the organic layer was washed once with brine. The aqueous layer was saturated with solid NaCl and back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (2:1 petroleum ether/EtOAc) afforded (*S*,*S*)-**13a** (97 mg, 95%) as an inseparable mixture of the *Z*- and *E*-diastereomers: Colorless oil; $[\alpha]_D^{22}$ −45.8 (c 0.79, $CHCl_3$); IR (neat) 3008, 2938, 1693, 1424 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.13−7.35 (m, 5 H), 5.24−5.60 (m, 2 H), 5.08 (d, J = 15.1 Hz, 1 H), 4.62 (d, J = 6.9 Hz, 1 H), 4.58 (d, J = 6.9 Hz, 1 H), 4.17−4.28 (m, 1 H), 3.95 (d, J = 15.1 Hz, 1 H), 3.47−3.58 (m, 1 H), 3.34 (s, 3 H), 2.47−2.67 (m, 2 H), 2.23−2.45 (m, 2 H), 1.53 (d, J = 6.7 Hz, 3 H); δ (discernible signals for minor diastereomer) 5.03 (d, J = 15.1 Hz, 1 H), 1.62 (d, J = 6.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 172.6, 136.4, 128.6, 127.7, 127.4, 126.8, 125.2, 96.0, 71.7, 60.1, 55.7, 43.9, 37.8, 24.8, 12.9; δ (discernible signals for minor diastereomer) 172.4, 136.4, 128.7, 128.5, 127.4, 126.1, 44.0, 37.7, 30.4, 18.0; HRMS (ESI-QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{23}NO_3Na$ 312.1576; Found 312.1561.

The ratio of *Z*- and *E*-alkenes was found to be ~2.2:1, based on integration of the methyl doublets at δ 1.53 and δ 1.62 in the ^{1}H NMR spectrum.

(5*R*,6*R*)-1-Benzyl-6-(but-2-enyl)-5-(methoxymethoxy)-piperidin-2-one (13b). Compound (*R*,*R*)-**13b** was prepared from the lactol (*R*,*R*)-**14b** according to the two-step procedure described above for the preparation of (*S*,*S*)-**13a**. Wittig olefination of the lactol (*R*,*R*)-**14b** (200 mg, 0.81 mmol) with ethylidenetriphenylphosphorane (4 equiv, $Ph_3P^+EtBr^-$, KO^{t}Bu) gave the alkenol (*R*,*R*)-**15b**. Purification by chromatography (1:4 petroleum ether/EtOAc) afforded the alkenol (*R*,*R*)-**15b** (204 mg, 97%, dr ~ 4:1) together with triphenylphosphine oxide as an inseparable mixture. The alkenol was obtained as mixture of *Z*- and *E*-diastereomers in a 2.3:1 ratio [Ph_3PO signals are clearly distinguishable from the signals of **15b**; Ph_3PO signals appeared between 7.5 and 8.5 ppm].

(5R,6R)-1-Benzyl-6-(but-2-enyl)-5-hydroxypiperidin-2-one (15b). IR (CH_2Cl_2) 3359−3118, 3058, 1632 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.12−7.28 (m, 5 H), 5.39−5.58 (m, 2 H), 5.39 (d, J = 15.2 Hz, 1 H), 4.14−4.21 (br d, J = 3.8 Hz, 1 H), 3.86−3.95 (m, 1 H), 3.88 (d, J = 15.2 Hz, 1 H), 3.30−3.39 (m, 1 H), 2.32−2.67 (m, 4 H), 1.75−2.00 (m, 2 H), 1.58 (d, J = 6.2 Hz, 3 H); δ (discernible signals for minor diastereomer) 5.35 (d, J = 15.2 Hz, 1 H), 4.11−4.18 (br d, J = 3.9 Hz, 1 H), 2.19−2.31 (m, 1 H), 1.62 (d, J = 5.5 Hz, 3 H). The ratio of *Z*- and *E*-alkenes was found to be 2.3:1, based on integration of the methyl doublets at δ 1.58 and δ 1.62 in the ^{1}H NMR spectrum.

In the second step, the alkenol (*R*,*R*)-**15b** (78 mg, 0.30 mmol) was converted to the OMOM derivative (*R*,*R*)-**13b**. Purification by chromatography (2:1 petroleum ether/EtOAc) afforded (*R*,*R*)-**13b** (72.6 mg, 81%) as an inseparable mixture of the *Z*- and *E*-diastereomers: Colorless oil; $[\alpha]_D^{22}$ +59.5 (c 1.09, $CHCl_3$); IR (neat) 3025, 2938, 2897, 1645, 1453, 1420 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.12−7.38 (m, 5 H), 5.33−5.65 (m, 3 H), 4.58 (d, J = 7.5 Hz, 1 H), 4.53 (d, J = 7.5 Hz, 1 H), 3.91 (d, J = 14.8 Hz, 1 H), 3.73−3.83 (m, 1 H), 3.33−3.45 (m, 1 H), 3.28 (s, 3 H), 2.35−2.74 (m, 4 H), 1.87−2.14 (m, 2 H), 1.60 (d, J = 6.7 Hz, 3 H); δ (discernible signals for minor diastereomer) 2.26 (ddd, J = 14.1, 7.1, 7.1 Hz, 1 H), 1.66 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 169.4, 137.3, 128.5, 127.8, 127.2, 126.9, 126.4, 95.6, 72.9, 57.9, 55.6, 48.4, 28.8, 26.8, 23.4, 12.9; δ (discernible signals for minor diastereomer) 169.5, 128.2, 127.8, 127.7, 58.2, 48.7, 32.5, 28.8, 23.3, 18.0; HRMS (ESI-QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{25}NO_3Na$ 326.1732; Found 326.1729.

The ratio of *Z*- and *E*-alkenes was found to be ~2.3:1, based on integration of the methyl doublets at δ 1.60 and δ 1.66 in the ^{1}H NMR spectrum.

(*R*)-1-Benzyl-5-(but-2-enyl)pyrrolidin-2-one (13c). To the alkenol (*S*,*S*)-**15a** (148 mg, 0.60 mmol) in DCE (10 mL) under argon at rt were added 4-(dimethylamino)pyridine (73 mg, 0.60 mmol), *N*,*N*-diisopropylethylamine (0.63 mL, 3.6 mmol), and phenoxythiocarbonyl chloride (0.25 mL, 1.8 mmol) successively, and the resulting solution was allowed to reflux, overnight. The reaction mixture was cooled to rt, diluted with CH_2Cl_2, and washed successively with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (1 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (4:1 petroleum ether/EtOAc) gave the corresponding thiocarbonate (151 mg, 66%) as an inseparable mixture of *Z*- and *E*-diastereomers.

(S,S)-1-Benzyl-5-(but-2-enyl)-4-(phenoxythiocarbonyloxy)-pyrrolidin-2-one. Orange oil; $[\alpha]_D^{22}$ +0.91 (c 1.43, $CHCl_3$); IR (neat) 3024, 2923, 1699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.19−7.47 (m, 8 H), 7.02−7.11 (m, 2 H), 5.49−5.77 (m, 2 H), 5.21−5.35 (m, 1 H), 5.12 (d, J = 15.2 Hz, 1 H), 4.06 (d, J = 15.2 Hz, 1 H), 3.74−3.85 (m, 1 H), 2.69−2.95 (m, 2 H), 2.50 (dd, J = 6.8, 6.8 Hz, 2 H), 1.61 (d, J = 6.7 Hz, 3 H); δ (discernible signals for minor diastereomer) 5.05 (d, J = 15.2 Hz, 1 H), 2.41 (dd, J = 6.7 Hz, 2 H), 1.66 (d, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 194.1, 171.6, 153.1, 135.9, 129.6, 128.8, 127.9, 127.8, 127.7, 123.5, 121.7, 77.6, 59.3, 44.1, 37.4, 25.0, 13.0; δ (discernible signals for minor diastereomer) 194.0, 171.6, 136.0, 129.9, 128.7, 127.9, 127.6, 124.4, 59.4, 37.3, 30.6, 18.1. The ratio of *Z*- and *E*-thiocarbonates was found to be ~2.2:1, based on integration of the benzylic methylene protons at δ 5.12 and δ 5.05 in the ^{1}H NMR spectrum.

To a mixture of AIBN (13 mg, 0.08 mmol) in degassed toluene (2 mL) at rt was added a solution of the thiocarbonate (151 mg, 0.40 mmol) in degassed toluene (4 mL) via cannula, followed by Bu_3SnH (0.22 mL, 0.79 mmol). The reaction mixture was allowed to stir at 100 °C (oil bath) for 2 h, and cooled to rt. Toluene was evaporated under reduced pressure, and the crude residue was diluted with EtOAc. Aqueous KF (4 mL, 10% w/v) was added, and the biphasic mixture was vigorously stirred for 30 min. The solution was vacuum filtered through a pad of Celite, and the two layers were separated. The

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aqueous layer was re-extracted into EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (1:1 petroleum ether/Et_2O then 1:2 petroleum ether/Et_2O) afforded the alkene (*R*)-**13c** (59.4 mg, 65.5%) as an inseparable mixture of *Z*- and *E*-diastereomers: Colorless oil; $[\alpha]_D^{22}$ −31.0 (*c* 0.72, $CHCl_3$); IR (neat) 3025, 2922, 2857, 1686, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.12−7.29 (m, 5 H), 5.36−5.59 (m, 1 H), 5.10−5.24 (m, 1 H), 4.97 (d, *J* = 15.1 Hz, 1 H), 3.89 (d, *J* = 15.0 Hz, 1 H), 3.33−3.46 (m, 1 H), 2.15−2.48 (m, 3 H), 1.86−2.13 (m, 2 H), 1.57−1.74 (m, 1 H), 1.51 (d, *J* = 6.7 Hz, 3 H); δ (discernible signals for minor diastereomer) 4.93 (d, *J* = 14.8 Hz, 1 H), 1.57 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (diastereomeric signals are not distinguishable) 175.1(5), 175.1(1), 136.7, 136.6(7), 128.5(6), 128.5(4), 129.2, 127.9(3), 127.9(2), 127.5, 127.4, 127.3, 124.9, 124.1, 56.5, 35.8, 30.1, 30.0(9), 30.0(6), 23.4, 23.1, 18.0, 13.0; HRMS (ESI-QTOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{15}H_{19}NONa$ 252.1364; Found 252.1354.

The ratio of *Z*- and *E*-alkenes was found to be ∼1.2:1, based on the integration of benzylic methylene protons at δ 4.97 and δ 4.93 in the ^1H NMR spectrum.

(*S*)-1-Benzyl-6-(but-2-enyl)piperidin-2-one (13d). Compound (*S*)-**13d** was prepared from the alkenol (*R*,*R*)-**15b** according to the two-step procedure described above for the preparation of (*R*)-**13c**. The alkenol (*R*,*R*)-**15b** (136 mg, 0.52 mmol) was first treated with phenoxythiocarbonyl chloride (0.22 mL, 1.56 mmol) to form the corresponding thiocarbonate derivative. Purification by chromatography (2:1 petroleum ether/EtOAc) gave the thiocarbonate (186 mg, 90%) as an inseparable mixture of *Z*- and *E*-diastereomers.

(5R,6R)-1-Benzyl-6-(but-2-enyl)-5-(phenoxythiocarbonyloxy)-piperidin-2-one. Orange oil; $[\alpha]_D^{23}$ +24.6 (*c* 0.74, $CHCl_3$); IR (neat) 3028, 2957, 2936, 1650, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.28−7.37 (m, 2 H), 7.11−7.28 (m, 6 H), 6.93−7.00 (m, 2 H), 5.42−5.60 (m, 1 H), 5.21−5.42 (m, 3 H), 3.99 (d, *J* = 15.2 Hz, 1 H), 3.59−3.74 (m, 1 H), 2.48−2.73 (m, 2 H), 2.43 (t, *J* = 6.9 Hz, 2 H), 2.24−2.39 (m, 1 H), 1.99−2.13 (m, 1 H), 1.53 (dd, *J* = 6.8, 0.6 Hz, 3 H); δ (discernible signals for minor diastereomer) 4.00 (d, *J* = 15.2 Hz, 1 H), 1.59 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 193.7, 169.0, 153.1, 136.8, 129.5, 128.6, 127.7, 127.4, 127.3, 126.6, 125.1, 121.7, 78.0, 56.5, 47.8, 28.2, 27.1, 22.2, 12.9; δ (discernible signals for minor diastereomer) 193.7, 169.1, 136.9, 129.3, 125.9, 56.9, 47.9, 32.9, 28.1, 18.0. The ratio of *Z*- and *E*-thiocarbonates was found to be ∼2.3:1, based on the integration of methyl doublets at δ 1.53 and δ 1.59 in the ^1H NMR spectrum.

The above thiocarbonate derivative (186 mg, 0.47 mmol) was reduced with Bu_3SnH (0.26 mL, 0.93 mmol) in the presence of AIBN (16 mg, 0.1 mmol) to form (*S*)-**13d**. Purification by chromatography (2:1 petroleum ether/EtOAc) afforded (*S*)-**13d** (76.5 mg, 67%) as an inseparable mixture of *Z*- and *E*-diastereomers: Colorless oil; $[\alpha]_D^{22}$ +41.4 (*c* 0.85, $CHCl_3$); IR (neat) 3022, 2947, 1642, 1496, 1466, 1450, 1415, 1341, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.17−7.33 (m, 5 H), 5.44−5.61 (m, 1 H), 5.39 (d, *J* = 15.1 Hz, 1 H), 5.16−5.29 (m, 1 H), 3.97 (d, *J* = 15.1 Hz, 1 H), 3.21−3.35 (m, 1 H), 2.09−2.53 (m, 4 H), 1.62−1.98 (m, 4 H), 1.58 (d, *J* = 6.8 Hz, 3 H); δ (discernible signals for minor diastereomer) 5.37 (d, *J* = 15.1 Hz, 1 H), 3.94 (d, *J* = 15.1 Hz, 1 H), 1.62 (dd, *J* = 6.5, 1.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 170.2, 137.6, 128.4, 127.5, 127.0, 126.7, 125.4, 55.1, 47.2, 31.9, 29.7, 26.2, 17.2, 12.8; δ (discernible signals for minor diastereomer) 170.2, 128.5, 126.9, 126.3, 47.2, 35.4, 31.8, 26.0, 17.8, 17.0; HRMS (ESI-QTOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{16}H_{21}NONa$ 266.1521; Found 266.1527.

The ratio of *Z*- and *E*-alkenes was ∼2.7:1, based on the integration of benzylic methylene signals at δ 3.97 and δ 3.94 in the ^1H NMR spectrum.

General Procedure for the Wacker Oxidation. $PdCl_2$ (0.2 mmol) was weighed into the reaction flask, and DMF/H_2O (5 mL, 1:1 v/v) was added. To the above brown color suspension was then added CuCl (1 mmol), and the mixture was stirred under O_2 (1 atm, balloon) for 1 h at rt. The alkene (1 mmol) was dissolved in DMF (2.5 mL) and was transferred into the above solution via syringe, followed by H_2O (2.5 mL). The resulting reddish brown solution was then stirred at 55 °C (oil bath) under an O_2 atmosphere for 24 h. The reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. CH_2Cl_2 was evaporated on the rotatory evaporator, followed by Kugelrohr distillation of the resulting mixture to remove DMF and H_2O. In order to remove the residual Pd-Cu color impurities from the crude product, it was dissolved in toluene (10 mL), NaBr (2.5 g) was added, and the resulting suspension was refluxed for 1 h. The reaction mixture was filtered through a pad of Celite, and the solvent was removed under reduced pressure. The crude residue was purified by chromatography.

Lactam Ketones 7a and 16a from Wacker Oxidation of (*S*,*S*)-13a. Wacker oxidation of (*S*,*S*)-**13a** (49 mg, 0.17 mmol) according to the general procedure afforded the ketones **7a** and **16a**. Purification by chromatography (1:2 petroleum ether/EtOAc) gave **7a** (44 mg, 87%) and **16a** (3.8 mg, 7%).

(4S,5S)-1-Benzyl-4-(methoxymethoxy)-5-(3-oxobutyl)pyrrolidin-2-one (7a). Pale yellow oil; $[\alpha]_D^{22}$ −21.5 (*c* 0.72, $CHCl_3$); IR (CH_2Cl_2) 3056, 2941, 2897, 1716, 1690, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.16−7.32 (m, 5 H), 4.95 (d, *J* = 15.1 Hz, 1 H), 4.60 (d, J = 6.8 Hz, 1 H), 4.55 (d, J = 6.8 Hz, 1 H), 4.24 (ddd, *J* = 6.1, 6.1, 6.1 Hz, 1 H), 3.96 (d, *J* = 15.1 Hz, 1 H), 3.51 (ddd, *J* = 6.1, 6.1, 6.1 Hz, 1 H), 3.30 (s, 3 H), 2.60 (d, *J* = 16.9, 6.9 Hz, 1 H), 2.49 (dd, *J* = 16.9, 5.7 Hz, 1 H), 2.41 (t, *J* = 7.4 Hz, 2 H), 2.04 (s, 3 H), 1.90 (td, *J* = 7.4, 6.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.3, 172.1, 136.3, 128.5, 127.8, 127.4, 95.7, 71.3, 59.1, 55.8, 43.9, 38.8, 37.5, 29.7, 20.8; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{17}H_{23}NO_4$ 305.1627; Found 305.1618.

(4S,5S)-1-Benzyl-4-(methoxymethoxy)-5-(2-oxobutyl)pyrrolidin-2-one (16a). Pale yellow oil; IR (CH_2Cl_2) 3055, 2983, 2933, 1712, 1692, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.14−7.35 (m, 5 H), 4.76 (d, *J* = 15.2 Hz, 1 H), 4.52 (d, *J* = 6.8 Hz, 1 H), 4.49 (d, *J* = 6.8 Hz, 1 H), 4.36 (m, 1 H), 4.21 (ddd, *J* = 9.0, 6.5, 4.8 Hz, 1 H), 4.12 (d, *J* = 15.2 Hz, 1 H), 3.29 (s, 3 H), 2.83 (dd, *J* = 17.1, 9.0 Hz, 1 H), 2.68 (dd, *J* = 17.1, 7.1 Hz, 1 H), 2.27−2.54 (m, 4 H), 0.99 (t, *J* = 7.5 Hz, 3 H). The minor ketone **16a** was not fully characterized due to insufficient amount of material.

Lactam Ketones 7b and 16b from Wacker Oxidation of (*R*,*R*)-13b. Wacker oxidation of (*R*,*R*)-**13b** (70 mg, 0.23 mmol) according to the general procedure gave the ketones **7b** and **16b**. Purification by chromatography (1:2 petroleum ether/EtOAc) afforded **7b** (64.6 mg, 88%) and **16b** (4.4 mg, 7%).

(5R,6R)-1-Benzyl-5-(methoxymethoxy)-6-(3-oxobutyl)piperidin-2-one (7b). Pale yellow oil; $[\alpha]_D^{22}$ +50.5 (*c* 1.74, $CHCl_3$); IR (neat) 2948, 2897, 1712, 1641, 1451 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.21−7.41 (m, 5 H), 5.36 (d, *J* = 14.9 Hz, 1 H), 4.59 (d, *J* = 6.8 Hz, 1 H), 4.54 (d, *J* = 6.8 Hz, 1 H), 4.00 (d, *J* = 14.9 Hz, 1 H), 3.78−3.88 (m, 1 H), 3.41 (ddd, *J* = 8.0, 4.9, 4.9 Hz, 1 H), 3.29 (s, 3 H), 2.46−2.74 (m, 4 H), 2.13 (s, 3 H), 1.86−2.17 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.7, 169.3, 137.2, 128.5, 127.9, 127.3, 95.3, 73.2, 56.9, 55.5, 48.6, 40.4, 29.8, 28.6, 23.1, 22.7; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{25}NO_4$ 319.1784; Found 319.1783.

(5R,6R)-1-Benzyl-5-(methoxymethoxy)-6-(2-oxobutyl)piperidin-2-one (16b). Pale yellow oil; IR (CH_2Cl_2) 3056, 2949, 1715, 1642, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12−7.31 (m, 5 H), 4.90 (d, *J* = 14.6 Hz, 1 H), 4.42 (d, *J* = 6.8 Hz, 1 H), 4.37 (d, *J* = 6.8 Hz, 1 H), 4.15 (m, 1 H), 4.04 (d, *J* = 14.6 Hz, 1 H), 3.80 (ddd, *J* = 10.0, 4.3, 4.3 Hz, 1 H), 3.19 (s, 3 H), 2.86 (dd, *J* = 17.1, 6.1 Hz, 1 H), 2.08−2.67 (m, 5 H), 1.78−2.0 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.6, 169.0, 137.3, 128.6, 128.3, 128.2, 127.4, 95.1, 71.3, 55.6, 53.9, 49.0, 42.2, 36.6, 29.3, 23.6. The minor ketone **16b** was not fully characterized due to insufficient amount of material.

Lactam Ketones 7c and 16c from Wacker Oxidation of (*R*)-13c. Wacker oxidation of (*R*)-**13c** (57.5 mg, 0.22 mmol) according to the general procedure afforded the ketones **7c** and **16c**. Purification by chromatography (1:2 petroleum ether/EtOAc, then 1:3 petroleum ether/EtOAc) gave **7c** (48 mg, 78%) and **16c** (2.6 mg, 5%).

(S)-1-Benzyl-5-(3-oxobutyl)pyrrolidin-2-one (7c). Colorless oil; $[\alpha]_D^{22}$ −58.7 (*c* 0.45, $CHCl_3$); IR (neat) 3031, 2934, 1716, 1683, 1492 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.14−7.28 (m, 5 H), 4.87 (d, *J* = 15.0 Hz, 1 H), 3.93 (d, *J* = 15.0 Hz, 1 H), 3.39 (dddd, *J* = 8.3,

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8.3, 5.4, 3.1 Hz, 1 H), 2.16−2.48 (m, 4 H), 2.02 (s, 3 H), 1.86−2.08 (m, 2 H), 1.47−1.62 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.1, 174.9, 136.6, 128.6, 128.0, 127.4, 56.0, 44.1, 38.0, 30.0, 29.9, 26.2, 23.4; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{15}H_{19}NO_2$ 245.1416; Found 245.1424.

*(S)-1-Benzyl-5-(2-oxobutyl)pyrrolidin-2-one (**16c**).* Pale yellow oil; IR (CH_2Cl_2) 3054, 2928, 1714, 1682, 1495 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17−7.35 (m, 5 H), 4.68 (d, J = 15.2 Hz, 1 H), 4.20 (d, J = 15.2 Hz, 1 H), 3.98 (ddd, J = 12.9, 8.3, 4.9 Hz, 1 H), 2.71 (dd, J = 15.0, 4.5 Hz, 1 H), 2.13−2.57 (m, 5 H), 1.56−1.69 (m, 1 H), 1.24−1.40 (m, 1 H), 0.97 (t, J = 7.3 Hz, 3 H). Compound **16c** was obtained as an inseparable mixture together with a minor amount of the E/Z enones resulting from a retro-Michael addition pathway in **16c** (see ^{1}H NMR spectrum of **16c** in the Supporting Information).

Lactam Ketones 7d and 16d from Wacker Oxidation of (*S*)-13d. Wacker oxidation of (*S*)-**13d** (81.4 mg, 0.33 mmol) according to the general procedure gave the ketones **7d** and **16d**. Purification by chromatography (1:2 petroleum ether/EtOAc) afforded **7d** (75.5 mg, 87%) and **16d** (6.1 mg, 7%).

*(S)-1-Benzyl-6-(3-oxobutyl)piperidin-2-one (**7d**).* Pale yellow oil; $[\alpha]_D^{23}$ +68.3 (c 0.58, $CHCl_3$); IR (neat) 2950, 2887, 1716, 1636, 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12−7.27 (m, 5 H), 5.29 (d, J = 15.0 Hz, 1 H), 3.94 (d, J = 15.0 Hz, 1 H), 3.16−3.26 (m, 1 H), 2.35−2.45 (m, 2 H), 2.18−2.35 (m, 2 H), 2.03 (s, 3 H), 1.87−2.00 (m, 1 H), 1.50−1.88 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.1, 170.1, 137.6, 128.4, 127.7, 127.0, 54.5, 47.2, 39.2, 31.8, 29.9, 26.0, 25.4, 17.1; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{16}H_{21}NO_2$ 259.1572; Found 259.1564.

*(S)-1-Benzyl-6-(2-oxobutyl)piperidin-2-one (**16d**).* Pale yellow oil; IR (CH_2Cl_2) 3054, 2942, 1714, 1637, 1495 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12−7.27 (m, 5 H), 4.97 (d, J = 15.0 Hz, 1 H), 4.05 (d, J = 15.0 Hz. One H), 3.87−3.96 (m, 1 H), 2.63 (dd, J = 17.2, 4.4 Hz, 1 H), 2.55 (dd, J = 17.2, 8.1 Hz, 1 H), 2.38−2.47 (m, 2 H), 2.22 (q, J = 7.2 Hz, 2 H), 1.53−1.86 (m, 4 H), 0.93 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.7, 170.2, 137.6, 128.6, 127.8, 127.3, 51.8, 48.4, 45.5, 36.7, 31.8, 27.8, 17.3, 7.6. Compound **16d** was obtained as an inseparable mixture together with minor amount of the enone resulting from a retro-Michael addition pathway in **16d** (see ^{1}H NMR spectrum of **16d** in the Supporting Information).

1-Cyclohexyl-2-butene (17a). $Ph_3P^+EtBr^-$ (1.05 g, 2.8 mmol) was dried under vacuum at 110 °C for 1 h and cooled to rt. The above salt was suspended in THF (6 mL), and KO*t*-Bu (331 mg, 2.8 mmol) was added in one portion at 0 °C. A bright orange solution resulted, to which, after 30 min at 0 °C, was added the 2-cyclohexylacetaldehyde (235 mg, 1.9 mmol) in THF (2 mL) via cannula, and stirred for 1 h. Saturated aqueous NH_4Cl (3 mL) was added, and the THF was evaporated under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (petroleum ether) to afford **17a** (141 mg, 55%) as an inseparable mixture of *Z*- and *E*-diastereomers: Colorless oil; IR (CH_2Cl_2) 2925, 2853, 1449 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (*Z*-**17a**) 5.34−5.54 (m, 2 H), 1.93 (dd, J = 6.7, 6.7 Hz, 2 H), 1.62−1.77 (m, 5 H), 1.59 (d, J = 6.2 Hz, 3 H), 1.08−1.37 (m, 4 H), 0.81−1.00 (m, 2 H); δ (discernible signals for *E*-**17a**) 1.86 (dd, J = 6.7, 6.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (*Z*-**17a**) 129.4, 124.2, 38.3, 34.6, 33.2, 26.6, 26.4, 12.8; δ (discernible signals for *E*-**17a**) 40.6, 38.1, 33.1, 17.9. Compound *Z*-**17a** has been reported[21] in the literature.

The ratio of *Z*- and *E*-alkenes was 5.5:1, respectively, based on integration of the methyl signals at δ 1.93 and δ 1.86 in the ^{1}H NMR spectrum.

6-Allyl-1-benzylpiperidin-2-one (17b). To the known[44] *N*-benzyl glutarimide (1.60 g, 7.87 mmol) in THF (40 mL) at −78 °C under Ar was added $LiBEt_3H$ (11.8 mL, 1 M in THF), and the solution was stirred at the same temperature for 30 min. The reaction mixture was quenched with saturated $NaHCO_3$ and was allowed to warm to 0 °C. Aqueous H_2O_2 (6 mL, 30%) was added dropwise, and the resulting solution was stirred at the same temperature for 30 min before allowing it to warm to rt. The solvent was evaporated under reduced pressure, and the crude residue was diluted with CH_2Cl_2. The two layers were separated, and the aqueous layer was back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude *N,O*-acetal (1.60 g) was obtained as a white solid, which, without any further purification, was subjected to allylation in the next step.

1-Benzyl-6-hydroxypiperidin-2-one. IR (CH_2Cl_2) 3550−3115, 2958, 1617, 1483 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20−7.24 (m, 5 H), 5.12 (d, J = 14.9 Hz, 1 H), 4.90 (ddd, J = 6.8, 3.4, 3.4 Hz, 1 H), 4.30 (d, J = 14.9 Hz, 1 H), 3.61 (br d, J = 6.8 Hz, 1 H), 2.51 (ddd, J = 17.6, 9.0, 4.4 Hz, 1 H), 2.38 (ddd, J = 17.6, 10.4, 6.2 Hz, 1 H), 1.99−2.17 (m, 1 H), 1.62−1.96 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 137.6, 128.6, 128.1, 127.3, 78.8, 46.9, 32.4, 30.9, 15.8.

To the above *N,O*-acetal (1.60 g) in dry CH_2Cl_2 (30 mL) under Ar was added allyltrimethylsilane (2.48 mL, 15.6 mmol), and the solution was cooled to −78 °C. $BF_3{\cdot}Et_2O$ (1.96 mL, 15.6 mmol) was added dropwise to the above mixture, and the resulting solution was stirred at the same temperature for 30 min before allowing it to warm to rt, overnight. The reaction mixture was cooled to 0 °C, and saturated $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (1:2 petroleum ether/Et_2O then 1:3 petroleum ether/Et_2O) afforded **17b** (1.50 g, 83% over two steps) as a colorless oil: IR (neat) 2949, 1636, 1468 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17−7.33 (m, 5 H), 5.54−5.70 (m, 1 H), 5.38 (d, J = 15.2 Hz, 1 H), 5.00−5.12 (m, 2 H), 3.96 (d, J = 15.2 Hz, 1 H), 3.32 (ddd, J = 13.7, 4.6, 4.6 Hz, 1 H), 2.37−2.51 (m, 3 H), 2.17−2.31 (m, 1 H), 1.60−1.95 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 137.5, 133.9, 128.4, 127.6, 127.0, 118.0, 54.7, 47.2, 36.7, 31.8, 26.1, 17.0. (*R*)-**17b** has been reported[22] in the literature.

1-Benzyl-6-(prop-1-enyl)piperidin-2-one (17d). The alkene **17d** was prepared from the allyl δ-lactam **17b** (65 mg, 0.28 mmol) according to the procedure described for the preparation of **11**. Purification by chromatography (2:1 petroleum ether/EtOAc) afforded **30** (58 mg, 89%) as an inseparable mixture of *Z*- and *E*-diastereomers: Brown oil: IR (neat) 2945, 2920, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15−7.33 (m, 5 H), 5.42 (d, J = 14.8 Hz, 1 H), 5.29−5.68 (m, 2 H), 3.77 (d, J = 14.8 Hz, 1 H), 3.69−3.80 (m, 1 H), 2.36−2.55 (m, 2 H), 1.71 (d, J = 6.2 Hz, 3 H), 1.60−1.95 (m, 4 H); δ (discernible signals for the minor diastereomer) 4.07−4.16 (m, 1 H), 1.49 (dd, J = 6.9, 0.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 170.1, 137.8, 130.5, 128.4, 128.1, 127.9, 127.0, 57.7, 47.0, 32.2, 29.4, 17.5 (4), 17.5 (0); δ (discernible signals for the minor diastereomer) 137.7, 130.9, 128.0, 52.3, 46.8, 32.4, 29.6, 18.4, 12.8; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{15}H_{19}NO$ 229.1467; Found 229.1462.

The ratio of *E*- and *Z*-**17d** could not be determined due to the extensive overlap of signals in the ^{1}H NMR spectrum.

Ketones 18a and 19a from Wacker Oxidation of 17a. Wacker oxidation of **17a** (45 mg, 0.33 mmol) according to the general procedure afforded the ketones **18a** and **19a**. Purification by chromatography (10:1 petroleum ether/Et_2O) gave an inseparable mixture of **18a** and **19a** (15.3 mg) as a colorless oil in 30% combined yield. The ratio of the ketones **18a** and **19a** was found to be 1.6:1, based on the integration of the methyl singlet at δ 2.11 (**18a**) and the methyl triplet at δ 1.02 (**19a**) in the ^{1}H NMR spectrum.

*4-Cyclohexylbutan-2-one (**18a**) and 1-Cyclohexylbutan-2-one (**19a**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ (extensive overlap of signals in the cyclohexyl ring region of **18a** and **19a**) 0.78−0.98 (m), 1.10−1.33 (m), 1.54−1.74 (m); δ (discernible signals for **18a**) 2.41 (t, J = 7.5 Hz, 2 H), 2.11 (s, 3 H), 1.40−1.50 (m, 2 H); δ (discernible signals for **19a**) 2.37 (q, J = 7.3 Hz, 2 H), 2.25 (d, J = 6.9 Hz, 2 H), 1.02 (t, J = 7.3 Hz, 3 H). The ketones **18a**[23] and **19a**[24] have been reported in the literature.

Compounds 18b and 19b from Wacker Oxidation of 17b. Wacker oxidation of **17b** (66 mg, 0.29 mmol) according to the general procedure gave **18b** and **19b**. Purification by chromatography (1:4 petroleum ether/EtOAc) afforded a mixture of **18b** and **19b** (60.2 mg) as a colorless oil in 85% combined yield. The ratio of **18b** and **19b** was found to be 1:3.5, respectively, based on the integration of the benzylic

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proton signals at δ 5.32 (**18b**) and δ 5.00 (**19b**) in the ^{1}H NMR spectrum.

*3-(1-Benzyl-6-oxopiperidin-2-yl)propanal (**18b**) and 1-Benzyl-6-(2-oxopropyl)piperidin-2-one (**19b**).* IR (CH_2Cl_2) 2952, 1717, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (extensive overlap of signals in **18b** and **19b**) 7.08−7.37 (m, 5 H), 2.55−2.76 (m), 2.31−2.54 (m), 1.55−1.92 (m); δ (discernible signals for **18b**) δ 9.68 (s, 1 H), 5.32 (d, J = 15.3 Hz, 1 H), 3.99 (d, J = 15.3 Hz, 1 H), 3.22−3.32 (m, 1 H); δ (discernible signals for **19b**) 5.00 (d, J = 15.1 Hz, 1 H), 4.08 (d, J = 15.1 Hz, 1 H), 3.86−3.98 (m, 1 H), 2.00 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (**18b**) 170.1, 137.4, 128.4, 127.7, 127.1, 54.5, 47.3, 39.8, 31.8, 26.0, 23.8, 17.1; δ (**19b**) 170.0, 137.3, 128.5, 127.6, 127.2, 51.4, 48.2, 46.5, 31.7, 30.4, 27.6, 17.1; Compound **19b**[25] has been reported in the literature.

1-Cyclohexylpropan-2-one (19c). Wacker oxidation of allylcyclohexane (50 mg, 0.40 mmol) according to the general procedure gave the ketone **19c**. Purification by chromatography (petroleum ether) afforded the ketone **19c** (39 mg, 68%) as a colorless oil: IR (neat) 2925, 2853, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.28 (d, J = 6.8 Hz, 2 H, CH_2C(O)Me), 2.11 (s, 3 H), 1.58−1.89 (m, 5 H), 1.03−1.35 (m, 4 H), 0.82−0.10 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209, 51.5, 33.9, 33.2, 30.5, 26.2, 26.1. Compound **19c** has been reported[26] in the literature.

General Procedure for the Alkylidene Carbene Generation-C−H Insertion. *Conditions A*: To the yellow colored solution of trimethylsilyldiazomethane (0.20 mmol, 2.0 M in hexane) in THF (2.5 mL) under argon at −78 °C was added *n*-BuLi (0.19 mmol, 1.85 M in hexane) dropwise. The resulting yellow-orange solution was stirred at −78 °C for 45 min, and the appropriate lactam ketone (0.1 mmol) in THF (1 mL) was added dropwise via cannula (rinsed with 0.5 mL THF). At this time, the color of the solution changed from yellow-orange to brown. After stirring the reaction mixture for 30 min at −78 °C, the reaction temperature was gradually raised to 0 °C by itself. The solution was stirred for another 30 min at 0 °C, saturated aqueous NH_4Cl (1 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 5 mL). The aqueous layer was saturated with solid NaCl and back-extracted into EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography.

Conditions B: The lithiotrimethylsilyldiazomethane anion (3.0 equiv) was generated according to the same procedure described for conditions A. However, after the addition of ketone, the reaction mixture was stirred at −78 °C for 20 min and was directly allowed to warm to 0 °C (ice−water bath). The solution was stirred for 30 min at 0 °C, and saturated aqueous NH_4Cl (1 mL) was added. A similar workup procedure to that of conditions A was used for isolation of products.

Conditions C: The lithiotrimethylsilyldiazomethane anion (1.9 equiv) was generated according to the same procedure described for conditions A. However, after the addition of ketone, the reaction mixture was stirred at −78 °C for 20 min and was directly allowed to warm to 0 °C (ice−water bath). The evolution of N_2 gas was observed during the warming process. The solution was stirred for 30 min at 0 °C, and saturated aqueous NH_4Cl (1 mL) was added. A similar workup procedure to that of conditions A was used for isolation of products.

Compounds 20a, 21, 22, and 23 from Alkylidene Carbene Generation-C−H Insertion Reaction of (*S,S*)-7a. Alkylidene carbene generation-C−H insertion of (*S,S*)-**7a** (34.3 mg, 0.11 mmol) according to the general procedure described under conditions A gave **20a**, **21**, and **22**. Purification by chromatography (2:1 petroleum ether/EtOAc, then 1:1 petroleum ether/EtOAc) afforded the spirolactam **20a** (13.5 mg, 45%) and the homologated ketones **21** (6.7 mg, 19%) and **22** (2.7 mg, 8%). When the alkylidene carbene generation-C−H insertion of (*S,S*)-**7a** (19.2 mg, 0.06 mmol) was conducted under conditions C according to the general procedure, the spirolactam **20a** (9.8 mg, 53%) and the β-elimination product **23** (~1 mg, 5%) were obtained.

*(4S,5R)-1-Benzyl-4-(methoxymethoxy)-7-methyl-1-azaspiro[4,4]-non-6-ene-2-one (**20a**).* $[\alpha]_D^{23}$ +79.0 (c 0.97, $CHCl_3$); IR (CH_2Cl_2) 3061, 3032, 2924, 2849, 1694, 1663, 1605, 1495 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10−7.30 (m, 5 H), 4.83−4.89 (m, 1 H), 4.57 (d, J = 6.7 Hz, 1 H), 4.53 (d, J = 6.7 Hz, 1 H), 4.35 (d, J = 15.0 Hz, 1 H), 4.19 (d, J = 15.0 Hz, 1 H), 4.04 (dd, J = 7.5, 7.5 Hz, 1 H), 3.26 (s, 3 H), 2.62 (dd, J = 16.2, 7.5 Hz, 1 H), 2.35−2.48 (m, 2 H), 2.09−2.18 (m, 2 H), 1.67 (s, 3 H), 1.53 (ddd, J = 14.4, 7.2, 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 147.5, 138.8, 128.3, 127.7, 127.0, 126.0, 95.7, 79.6, 77.0, 55.4, 43.1, 36.8, 35.9, 28.0, 16.8; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{18}H_{23}NO_3$ 301.1678; Found 301.1685.

*(4S,5S)-1-Benzyl-4-(methoxymethoxy)-5-(4-oxopentyl)pyrrolidin-2-one (**21**).* Colorless oil; $[\alpha]_D^{22}$ −5.4 (c 1.21, $CHCl_3$); IR (CH_2Cl_2) 3056, 2953, 1713, 1690, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12−7.30 (m, 5 H), 5.00 (d, J = 15.1 Hz, 1 H), 4.67 (d, J = 6.9 Hz, 1 H), 4.61 (d, J = 6.9 Hz, 1 H), 4.23−4.32 (m, 1 H), 4.00 (d, J = 15.1 Hz, 1 H), 3.45−3.53 (m, 1 H), 3.36 (s, 3 H), 2.63 (dd, J = 16.9, 6.3 Hz, 1 H), 2.55 (dd, J = 16.9, 5.2 Hz, 1 H), 2.37 (t, J = 6.9 Hz, 2 H), 2.09 (s, 3 H), 1.43−1.80 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.1, 172.6, 136.5, 128.7, 127.5, 96.0, 71.5, 60.2, 56.0, 44.1, 43.4, 37.9, 29.9, 26.4, 19.4; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{18}H_{25}NO_4$ 319.1784; Found 319.1782.

*(4S,5S)-1-Benzyl-4-(methoxymethoxy)-5-(3-oxopentyl)pyrrolidin-2-one (**22**).* Colorless oil; $[\alpha]_D^{22}$ −13.0 (c 0.71, $CHCl_3$); IR (CH_2Cl_2) 3056, 2941, 1712, 1691, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12−7.30 (m, 5 H), 4.93 (d, J = 15.0 Hz, 1 H), 4.58 (d, J = 6.7 Hz, 1 H), 4.53 (d, J = 6.7 Hz, 1 H), 4.21 (m, 1 H), 3.93 (d, J = 15.0 Hz, 1 H), 3.49 (m, 1 H), 3.28 (s, 3 H), 2.58 (dd, J = 16.9, 6.9 Hz, 1 H), 2.47 (dd, J = 16.9, 6.0 Hz, 1 H), 2.36 (t, J = 7.2 Hz, 2 H), 2.29 (q, J = 7.3 Hz, 2 H), 1.89 (m, 2 H), 0.96 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.3, 172.3, 136.4, 128.7, 128.0, 127.6, 95.9, 71.4, 59.4, 55.9, 44.1, 37.7, 37.6, 35.9, 21.0, 7.8; HRMS (ESI-QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{25}NO_4Na$ 342.1681; Found 342.1683.

*(S)-1-Benzyl-7-methyl-1-azaspiro[4,4]non-3,6-diene-2-one (**23**).* IR (CH_2Cl_2) 3054, 2919, 1680, 1424 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26−7.38 (m, 5 H, Ar-H), 6.93 (d, J = 5.8 Hz, 1 H), 6.16 (d, J = 5.8 Hz, 1 H), 4.77−4.81 (m, 1 H), 4.67 (d, J = 15.5 Hz, 1 H), 4.36 (d, J = 15.5 Hz, 1 H), 2.33−2.42 (m, 2 H), 2.09−2.21 (m, 1 H), 1.81−1.93 (m, 1 H), 1.81 (d, J = 0.9 Hz, 3 H). Compound **23** was not fully characterized due to insufficient amount of material.

Compounds 20b and 24 from Alkylidene Carbene Generation-C−H Insertion of (*R,R*)-7b. Alkylidene carbene generation-C−H insertion of (*R,R*)-**7b** (34.2 mg, 0.11 mmol) according to the general procedure under conditions B afforded the spirolactam **20b** and the bicyclic alcohol **24**. Purification by chromatography (1:1 petroleum ether/EtOAc then EtOAc) gave **20b** (8.0 mg, 24%) and **24** (11.2 mg, 33%). When alkylidene carbene generation-C−H insertion of (*R,R*)-**7b** (26 mg, 0.08 mmol) was conducted under conditions C according to the general procedure, the spirolactam **20b** (18.5 mg, 72%) was obtained exclusively.

*(5S,10R)-6-(Benzyl)-2-methyl-10-(methoxymethoxy)-6-azaspiro-[4,5]dec-1-ene-7-one (**20b**).* Colorless oil; $[\alpha]_D^{22}$ −84.1 (c 0.8, $CHCl_3$); IR (neat) 3033, 2943, 2850, 1636 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08−7.36 (m, 5 H), 4.89−4.96 (m, 1 H), 4.65 (d, J = 6.9 Hz, 1 H), 4.61 (d, J = 15.5 Hz, 1 H), 4.36 (d, J = 6.9 Hz, 1 H), 3.73 (dd, J = 9.1, 4.1 Hz, 1 H), 3.32 (s, 3 H), 2.44−2.72 (m, 2 H), 2.18−2.41 (m, 3 H), 1.90−2.10 (m, 2 H), 1.71−1.85 (m, 1 H), 1.71 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 145.9, 139.8, 128.1, 127.2, 126.9, 126.4, 95.5, 77.7, 76.4, 55.6, 46.3, 36.4, 31.3, 29.5, 23.7, 16.6; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{19}H_{25}NO_3$ 315.1834; Found 315.1829.

*(1R,5R,9R)-6-Benzyl-2-hydroxy-9-(methoxymethoxy)-2-methyl-6-aza-bicyclo[3.2.2]nonan-7-one (**24**).* Colorless oil; $[\alpha]_D^{22}$ −6.5 (c 0.41, $CHCl_3$); IR (CH_2Cl_2) 3548−3133, 3047, 2950, 1646 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07−7.33 (m, 5 H), 4.69 (d, J = 14.7 Hz, 1 H), 4.48 (d, J = 7.0 Hz, 1 H), 4.45 (d, J = 7.0 Hz, 1 H), 4.28 (d, J = 14.7 Hz, 1 H), 3.80 (ddd, J = 10.2, 5.6, 4.5 Hz, 1 H), 3.39−3.46 (m, 1 H), 3.22 (s, 3 H), 2.60 (d, J = 6.5 Hz, 1 H), 2.40 (ddd, J = 15.2, 10.5, 6.5 Hz, 1 H), 1.88−1.99 (m, 1 H), 1.60−1.77 (m, 3 H), 1.50 (ddd, J = 14.2, 7.1, 3.5 Hz, 1 H), 1.24 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4, 137.1, 128.6, 128.3, 127.6, 96.2, 73.2, 71.2, 55.7, 55.5, 53.4, 49.4,

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34.5, 31.1, 29.8, 23.9. HRMS (ESI-QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{25}NO_4Na$ 342.1681; Found 342.1671.

(*R*)-1-Benzyl-7-methyl-1-azaspiro[4,4]non-6-ene-2-one (20c). Alkylidene carbene generation-C−H insertion of the lactam ketone (*S*)-**7c** (16 mg, 0.06 mmol) according to the general procedure under conditions C gave the spirolactam **20c**. Purification by chromatography (1:2 petroleum ether/EtOAc) afforded **20c** (11.9 mg, 76%) as a colorless oil: $[\alpha]_D^{23}$ +110.3 (*c* 1.17, $CHCl_3$); IR (neat) 3050, 2970, 2938, 2922, 2851, 1682, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10−7.25 (m, 5 H), 4.88−4.93 (m, 1 H), 4.26 (d, J = 15.7 Hz, 1 H), 4.20 (d, J = 15.7 Hz, 1 H), 2.45 (dd, J = 16.4, 8.1 Hz, 1 H), 2.37 (dd, J = 16.4, 6.9 Hz, 1 H), 2.14 (dd, J = 6.8, 6.8 Hz, 2 H), 1.92 (dd, J = 7.7, 7.7 Hz, 2 H), 1.77−1.85 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5, 144.7, 139.2, 128.2, 128.1, 127.6, 126.8, 76.5, 43.2, 35.3, 35.0, 33.4, 30.2, 16.6; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{16}H_{19}NO$ 241.1467; Found 241.1471.

(*S*)-6-(Benzyl)-2-methyl-6-azaspiro[4,5]dec-1-ene-7-one (20d). Alkylidene carbene generation-C−H insertion of the lactam ketone (*S*)-**7d** (43 mg, 0.17 mmol) according to the general procedure under conditions C gave the spirolactam **20d**. Purification by chromatography (1:1 petroleum ether/EtOAc) afforded **20d** (26.7 mg, 62%) as a pale yellow oil: $[\alpha]_D^{22}$ −88.7 (*c* 0.87, $CHCl_3$); IR (CH_2Cl_2) 3053, 2947, 1628, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.21−7.30 (m, 2 H), 7.13−7.21 (m, 3 H), 5.02−5.07 (m, 1 H), 4.66 (d, J = 15.4 Hz, 1 H), 4.34 (d, J = 15.4 Hz, 1 H), 2.40−2.60 (m, 2 H), 2.13−2.34 (m, 2 H), 1.72−2.06 (m, 6 H), 1.68 (d, J = 1.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 142.7, 140.0, 130.0, 128.1, 127.0, 126.3, 74.0, 46.2, 36.0, 35.6, 35.3, 18.2; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{17}H_{21}NO$ 255.1623; Found 255.1629.

(5*R*,10*S*)-6-(*p*-Methoxybenzyl)-10-(methoxymethoxy)-2-methyl-6-azaspiro[4,5]dec-1-ene-7-one (20e). Alkylidene carbene generation-C−H insertion of the lactam ketone (*S*,*S*)-**7d** (28 mg, 0.08 mmol) according to the general procedure under conditions C afforded the spirolactam **20d**. Purification by chromatography (1:2 petroleum ether/EtOAc) gave **20d** (15.1 mg, 55%) as a colorless oil: $[\alpha]_D^{23}$ +65.0 (*c* 1.40, $CHCl_3$); IR (CH_2Cl_2) 3024, 2900, 1636, 1629 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.07−7.15 (m, 2 H), 6.76−6.84 (m, 2 H), 4.90−4.96 (m, 1 H), 4.64 (d, J = 6.9 Hz, 1 H), 4.56 (d, J = 15.1 Hz, 1 H), 4.55 (d, J = 6.9 Hz, 1 H), 4.28 (d, J = 15.1 Hz, 1 H), 3.78 (s, 3 H), 3.71 (dd, J = 9.4, 4.1 Hz, 1 H), 3.32 (s, 3 H), 2.64 (ddd, J = 17.9, 6.4, 5.2 Hz, 1 H), 2.50 (ddd, J = 17.9, 9.3, 7.0 Hz, 1 H), 2.19−2.40 (m, 3 H), 1.89−2.08 (m, 2 H), 1.73−1.84 (m, 1 H), 1.74 (s, 3 H); ^{13}C NMR (CDCl3, 75 MHz) δ 169.6, 158.2, 147.7, 132.0, 128.4, 127.3, 113.5, 95.5, 77.6, 76.4, 55.6, 55.2, 45.7, 36.4, 31.3, 29.6, 23.7, 16.6; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{20}H_{27}NO_4$ 345.1940; Found 345.1944.

(*S*)-1-Benzyl-6-(pent-2-enyl)piperidin-2-one ((*S*)-32). Wittig olefination of the lactol (*R*,*R*)-**14b** (1.14 g, 4.61 mmol) with propylidenetriphenylphosphorane (4 equiv, Ph_3P^+*n*-$PrBr^-$, KO^tBu) was conducted similar to the procedure described for the preparation of alkenol (*S*,*S*)-**15a**. Purification by chromatography (1:2 petroleum ether/EtOAc) afforded an inseparable mixture of the alkenol **31** (1.10 g, 87.5%) and triphenylphosphine oxide as a white solid. The alkenol **31** was obtained as a mixture of *E*- and *Z*-diastereomers in a 1:5 ratio. The ratio of the two diastereomers was determined based on the integration of the methyl group signals at δ 0.85 and δ 0.92 in the ^1H NMR spectrum: ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.05−7.23 (m, 5 H), 5.24−5.51 (m, 3 H), 3.98−4.05 (br m, 1 H), 3.77−3.89 (m, 2 H), 2.08−2.60 (m, 4 H), 1.68−2.02 (m, 4 H), 0.85 (t, J = 7.5 Hz, 3 H); δ (discernible signals for minor diastereomer) 1.46−1.63 (m, 1 H), 0.92 (td, J = 7.3, 1.0 Hz, 3 H).

The alkene **32** was prepared from the alkenol **31** following a two-step (thiocarbonate formation−free-radical reduction) procedure described for the preparation of (*R*)-**13c**. In the first step, the alkenol **31** (1.10 g) was converted to the corresponding thiocarbonate derivative. Purification by chromatography (4:1 petroleum ether/EtOAc, then 1:2 petroleum ether/EtOAc) gave an inseparable diastereomeric mixture of the thiocarbonate (1.45 g, 88%) as an orange oil. The ratio of the two diastereomers cannot be determined due to the extensive overlap of the signals in the ^1H NMR spectrum: $[\alpha]_D^{22}$ +40.5 (*c* 1.30, $CHCl_3$); IR (CH_2Cl_2) 2965, 2933, 1646, 1591 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.37−7.45 (m, 2 H), 7.20−7.36 (m, 6 H), 7.02−7.09 (m, 2 H), 5.27−5.64 (m, 3 H), 5.44 (d, J = 15.1 Hz, 1 H), 4.04 (d, J = 15.1 Hz, 1 H), 3.68−3.80 (m, 1 H), 2.57−2.81 (m, 2 H), 2.31−2.57 (m, 3 H), 1.94−2.22 (m, 3 H), 0.96 (t, J = 7.6 Hz, 3 H); δ (discernible signals for minor diastereomer) 4.09 (d, J = 14.5 Hz, 1 H), 0.98 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 193.5, 168.8, 152.9, 136.6, 134.8, 129.3, 128.5, 127.5, 127.2, 126.5, 123.4, 121.5, 77.9, 56.5, 47.8, 28.0, 27.2, 22.0, 20.5, 13.9; δ (discernible signals for minor diastereomer) 168.9, 136.8, 136.2, 127.5, 127.2, 123.5, 56.9, 32.7, 25.4, 15.1, 13.3. HRMS (FD-TOF) m/z: $[M]^+$ Calcd for $C_{24}H_{27}NO_3S$ 409.1712; Found 409.1713.

The above thiocarbonate (1.45 g) was subjected to free-radical-mediated reduction in the next step to form **32**. Purification by chromatography (2:1 petroleum ether/EtOAc) afforded an inseparable *E*/*Z* mixture of **32** (850 mg, 67%, 52% from **14b**) as a colorless oil. The ratio of the two diastereomers cannot be determined due to the extensive overlap of the signals in the ^1H NMR spectrum: $[\alpha]_D^{22}$ +36.8 (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 2957, 2873, 1640, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 5.40−5.52 (m, 1 H), 5.41 (d, J = 15.1 Hz, 1 H), 5.10−5.23 (m, 1 H), 3.97 (d, J = 15.1 Hz, 1 H), 3.29 (ddd, J = 13.6, 4.4, 4.4 Hz), 2.33−2.54 (m, 3 H), 2.18−2.32 (m, 1 H), 2.00 (dq, J = 7.2, 7.2 Hz, 2 H), 1.79−1.94 (m, 1 H), 1.58−1.79 (m, 3 H), 0.93 (t, J = 7.5 Hz, 3 H); δ (discernible signals for minor diastereomer) 5.37 (d, J = 15.3 Hz, 1 H), 0.92 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 170.2, 137.6, 134.5, 128.4, 127.6, 127.0, 123.9, 55.2, 47.3, 31.9, 29.9, 26.2, 20.7, 17.2, 14.0; δ (discernible signals for minor diastereomer) 170.2, 137.5, 135.7, 126.9, 124.1, 55.1, 35.4, 31.8, 26.0, 25.4, 17.0, 13.5; HRMS (ESI-QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{23}NONa$ 280.1677; Found 280.1665.

Lactam Ketones 30 and 33 from Wacker Oxidation of 32. Wacker oxidation of **32** (511 mg, 1.98 mmol) according to the general procedure afforded the ketones **30** and **33**. Purification by chromatography (1:1 petroleum ether/EtOAc) gave **30** (411 mg, 76%) and **33** (49 mg, 8%).

(S)-1-Benzyl-6-(3-oxopentyl)piperidin-2-one (30). Colorless oil; $[\alpha]_D^{21}$ +64.1 (*c* 1.03, $CHCl_3$); IR (neat) 2941, 1713, 1636, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.13−7.28 (m, 5 H), 5.30 (d, J = 15.0 Hz, 1 H), 3.94 (d, J = 15.0 Hz, 1 H), 3.21 (ddd, J = 8.8, 8.8, 4.9 Hz, 1 H), 2.40 (t, J = 6.5 Hz, 2 H), 2.16−2.39 (m, 4 H), 1.89−2.04 (m, 1 H), 1.49−1.89 (m, 5 H), 0.97 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.9, 170.1, 137.7, 128.4, 127.8, 127.0, 54.6, 47.3, 37.9, 35.9, 31.8, 26.1, 25.6, 17.2, 7.7; HRMS (EI-double focusing sector filed) m/z: $[M]^+$ Calcd for $C_{17}H_{23}NO_2$ 273.1729; Found 273.1719.

1-Benzyl-6-(2-oxopentyl)piperidin-2-one (33). Colorless oil; IR (CH_2Cl_2) 3054, 2961, 2877, 1711, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.16−7.32 (m, 5 H), 5.02 (d, J = 15.0 Hz, 1 H), 4.08 (d, J = 15.0 Hz, 1 H), 3.90−3.99 (m, 1 H), 2.67 (dd, J = 17.0, 4.6 Hz, 1 H), 2.59 (dd, J = 17.0, 8.2 Hz, 1 H), 2.41−2.50 (m, 2 H), 2.23 (td, J = 7.4, 2.1 Hz, 2 H), 1.59−1.87 (m, 4 H), 1.52 (qt, J = 7.4, 7.4 Hz, 2 H), 0.86 (t, J = 7.4 Hz, 3 H). Compound **33** was obtained as an inseparable mixture together with a minor amount of the enone resulting from a retro-Michael addition pathway in **33** (see ^1H NMR spectrum of **33** in the Supporting Information).

(*S*)-6-(Benzyl)-2-ethyl-6-azaspiro[4,5]dec-1-ene-7-one (29). Alkylidene carbene generation-C−H insertion of the lactam ketone **30** (200 mg, 0.73 mmol) according to the general procedure under conditions C gave the spirolactam **29**. Purification by chromatography (1:1 petroleum ether/EtOAc) afforded **29** (117 mg, 60%) as a colorless oil: $[\alpha]_D^{22}$ +79.7 (*c* 1.45, $CHCl_3$); IR (neat) 2964, 2938, 2876, 2847, 1638, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.10−7.26 (m, 5 H), 4.98 (t, J = 1.6 Hz, 1 H), 4.69 (d, J = 15.4 Hz, 1 H), 4.25 (d, J = 15.4 Hz, 1 H), 2.37−2.58 (m, 2 H), 2.12−2.34 (m, 2 H), 1.66−2.03 (m, 8 H), 0.91 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 148.4, 139.9, 127.9, 127.7, 126.8, 126.1, 45.9, 35.9, 35.0, 33.4, 32.4, 23.9, 18.0, 11.7. HRMS (FD-TOF) m/z: $[M]^+$ Calcd for

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$C_{18}H_{23}NO$ 269.1780; Found 269.1790; HPLC: Chiralpak AD column (4.6 mm × 250 mm); 95:5 v/v hexane/*i*-PrOH; flow rate, 1.0 mL/min; λ_{max} = 220 nm; t_R (*R*-**29**) = 11.9 min and t_R (*S*-**29**) = 13.1 min; 99% *ee*. The retention times for (*R*)- and (*S*)-**29** were determined by injecting a sample of (±)-**29** for chiral HPLC analysis.

(*S*)-1-Benzyl-6-oxo-2-(3-oxopentyl)piperidine-2-carbaldehyde (28). Ozone-oxygen stream gas was bubbled into a solution of nonracemic (*S*)-(+)-**29** (381 mg, 1.41 mmol) in 4:1 v/v CH_2Cl_2 and MeOH (20 mL) at −78 °C for 2 min, at which time a pale blue color remained in the solution (TLC analysis showed complete conversion of **29**). The above solution was purged with argon, and triphenylphosphine (443 mg, 1.69 mmol) was added at −78 °C. The reaction mixture was gradually allowed to warm to rt over a period of 1 h and stirred for overnight. After evaporation of the solvent under reduced pressure, the crude product was purified by chromatography (Et_2O) to give (*S*)-(−)-**28** (377 mg, 89%) as a white solid: mp 84−86 °C; $[\alpha]_D^{22}$ −102.8 (*c* 1.45, $CHCl_3$); IR (CH_2Cl_2) 3067, 2979, 2941, 1732, 1715, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.25 (s, 1 H), 7.00−7.19 (m, 5 H, Ar-H), 4.80 (d, *J* = 15.5 Hz, 1 H), 4.03 (d, *J* = 15.5 Hz, 1 H), 2.26−2.52 (m, 2 H), 1.75−2.22 (m, 7 H), 1.45−1.70 (m, 3 H), 0.75 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.1, 200.2, 171.9, 138.5, 128.5, 128.1, 127.2, 70.4, 47.3, 35.5, 35.4, 32.3, 28.6, 26.4, 17.1, 7.6. HRMS (FD-TOF) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{23}NO_3$ 301.1678; Found 301.1669.

(*S*)-1-Benzyl-8-methyl-1-azaspiro[5,5]dec-7-ene-2,9-dione (35). To a mixture of KOH (203 mg, 3.62 mmol) in EtOH (4 mL) under argon at 0 °C was added a solution of the keto-aldehyde (*S*)-(−)-**28** (364 mg, 1.21 mmol) in 3:1 v/v EtOH and CH_2Cl_2 (8 mL) via cannula. The solution was stirred at 0 °C for 10 min before allowing it to warm to rt, and left for overnight. The reaction mixture was cooled to 0 °C, and saturated NH_4Cl was added. All the volatiles were evaporated under reduced pressure, and the crude residue obtained was diluted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (1:2 petroleum ether/EtOAc) afforded the enone (*S*)-(−)-**35** (328 mg, 96%) as a colorless thick oil: $[\alpha]_D^{22}$ −71.9 (*c* 0.62, $CHCl_3$); IR (CH_2Cl_2) 3055, 2955, 1678, 1638, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.11−7.32 (m, 5 H), 6.34 (s, 1 H), 4.66 (d, *J* = 15.8 Hz, 1 H), 4.52 (d, *J* = 15.8 Hz, 1 H), 2.23−2.67 (m, 5 H), 2.00−2.15 (m, 2 H), 1.80−1.98 (m, 3 H), 1.69 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.9, 170.4, 149.1, 138.9, 135.7, 128.1, 126.6, 126.5, 61.0, 46.6, 34.4, 32.1, 31.6, 31.2, 17.6, 15.6; HRMS (FD-TOF) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{21}NO_2$ 283.1572; Found 283.1569.

1-Benzyl-6-(2′-methoxyvinyl)-6-(3″-oxopentyl)piperidin-2-one (36). $Ph_3P^+CH_2(OMe)Cl^-$ (55 mg, 0.15 mmol) was dried under vacuum at 110 °C for 1 h and cooled to rt. The above salt was suspended in THF (1 mL), and it was cooled to 0 °C under argon. NaHMDS (0.15 mL, 1.0 M solution in toluene) was added to the above suspension, and a bright orange solution resulted. After 20 min at 0 °C, the keto-aldehyde (±)-**28** (15.5 mg, 0.05 mmol) in THF (1 mL) was added via cannula. The reaction mixture was stirred at 0 °C for 1 h, and then allowed to warm to rt and stirred for overnight. Saturated aqueous NH_4Cl was added, and THF was evaporated under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (2:1 petroleum ether/EtOAc) to afford (±)-**36** (11.5 mg, 68%) as a colorless oil: IR (CH_2Cl_2) 2939, 1715, 1638, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (*Z*-**36**) 7.10−7.31 (m, 5 H), 5.88 (d, *J* = 7.2 Hz, 1 H), 5.00 (d, *J* = 15.5 Hz, 1 H), 4.12 (d, *J* = 7.2 Hz, 1 H), 4.05 (d, *J* = 15.5 Hz, 1 H), 3.55 (s, 3 H), 2.33−2.62 (m, 2 H), 1.55−2.25 (m, 10 H), 0.84 (t, J = 7.3 Hz, 3 H); δ (discernible signals for *E*-**36**) 6.27 (d, *J* = 13.0 Hz, 1 H), 4.93 (d, *J* = 15.4 Hz, 1 H), 4.60 (d, *J* = 13.0 Hz, 1 H), 4.16 (d, *J* = 15.4 Hz, 1 H), 3.41 (s, 3 H), 0.86 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (*E*- and *Z*-**36**) 210.4, 209.9, 172.5, 172.2, 148.8, 147.3, 140.1, 139.7, 128.3, 128.1, 128.0, 126.6, 126.4, 109.1, 107.2, 63.5, 62.6, 60.3, 56.1, 47.0, 46.4, 36.7, 36.5, 35.5, 35.4, 34.0, 33.5, 32.8, 32.7, 32.6, 31.8, 17.3, 16.4, 7.6, 7.6. HRMS (FD-TOF) *m*/*z*: $[M]^+$ Calcd for $C_{20}H_{27}NO_3$ 329.1991; Found 329.1993.

The ratio of *Z*- and *E*-alkenes was 1.2:1, based on the integration of the olefin proton doublets at δ 5.88 and δ 6.27 in the ^1H NMR spectrum. The yield of **36** was found to vary widely (25−68%) in the subsequent experiments.

1-Benzyl-9-ethyl-7,9-dimethoxy-8-oxa-1-azaspiro[5,5]-decane-2-one (37). To the keto-aldehyde (±)-**28** (7.2 mg, 0.024 mmol) in CH_2Cl_2 and MeOH (0.8 mL, 1:1 v/v) under Ar at rt were successively added molecular sieves (10 mg, 4 Å) and camphor sulfonic acid (2.8 mg, 0.01 mmol), and the resulting solution was stirred for 10 min. The reaction mixture was cooled to 0 °C, and triethylamine (2 drops) was added. After stirring the mixture for 10 min, the solvent was evaporated under reduced pressure. Purification by chromatography (1:1 petroleum ether/EtOAc) afforded (±)-**37** (6.8 mg, 82%) as a mixture of two inseparable diastereomers: Colorless oil; IR (CH_2Cl_2) 3054, 2968, 1640, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.10−7.34 (m, 5 H), 5.08 (d, *J* = 16.0 Hz, 1 H), 4.52 (s, 1 H), 4.39 (d, *J* = 16.0 Hz, 1 H), 3.16 (s, 3 H), 2.81 (s, 3 H), 2.41−2.62 (m, 2 H), 2.18−2.38 (m, 2 H), 1.89−2.04 (m, 1 H), 1.40−1.88 (m, 7 H), 0.85 (t, *J* = 7.6 Hz, 3 H); δ (discernible signals for minor diastereomer) 3.53 (s, 3 H), 3.28 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major diastereomer) 172.5, 139.1, 128.2, 127.1, 126.5, 101.4, 97.9, 60.8, 55.6, 47.5, 44.5, 32.9, 29.5, 28.3, 28.1, 24.5, 16.8, 7.5; HRMS (FD-TOF) *m*/*z*: $[M]^+$ Calcd for $C_{20}H_{29}NO_4$ 347.2097; Found 347.2090.

The diastereomeric ratio of **37** was 18:1, based on the integration of the methyl group singlets at δ 3.16 and δ 3.53 in the ^1H NMR spectrum.

(6*S*,8*RS*)-1-Benzyl-8-methyl-9-oxa-1-azaspiro[5,6]undecane-2,10-dione (39). A solution of the enone (*S*)-(−)-**35** (240 mg, 0.85 mmol) in 95% ethanol (20 mL) was shaken for 8 h under hydrogen (40 psi, Parr) over 10% palladium on carbon (30 mg). The mixture was filtered through a pad of Celite, and the solvent was evaporated under reduced pressure. The crude product (242 mg), without further purification, was subjected to oxidation using PDC (320 mg, 0.85 mmol) in CH_2Cl_2 (15 mL) containing 3 Å crushed molecular sieves (300 mg) under Ar. The resulting brown solution was stirred at rt for 8 h, and then the reaction mixture was diluted with Et_2O. Celite and 2-propanol (0.5 mL) were added, the mixture was stirred for 15 min at rt and filtered, and the filtrate was evaporated. Purification by chromatography (1:2 petroleum ether/EtOAc) gave an inseparable mixture of the ketone **38** and the enone **35** (220 mg) as a colorless oil. The ratio of **38** and **35** was 7:1, based on the integration of the methyl doublets δ 0.89 and δ 0.95 (in **38**) and the methyl singlet at δ 1.69 (in **35**) in the ^1H NMR spectrum.

(6*S*,8*RS*)-1-Benzyl-8-methyl-1-azaspiro[5,6]decane-2,9-dione (38). IR (CH_2Cl_2) 2951, 1715, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.02−7.28 (m, 5 H), 4.80 (d, *J* = 16.6 Hz, 1 H), 4.69 (d, *J* = 16.6 Hz, 1 H), 2.05−2.73 (m, 7 H), 1.69−2.00 (m, 5 H), 1.44 (dd, *J* = 15.1, 2.9 Hz, 1 H), 0.89 (d, *J* = 6.5 Hz, 3 H); δ (discernible signals for minor diastereomer) 4.51 (d, *J* = 16.0 Hz, 1 H), 0.95 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 212.5, 170.7, 139.1, 128.4, 126.7, 126.2, 59.2, 45.8, 42.7, 41.4, 41.2, 35.3, 32.2, 31.0, 16.4, 13.9; δ (minor diastereomer) 210.3, 170.9, 139.0, 128.3, 126.5, 126.1, 59.5, 44.4, 40.7, 37.6, 36.0, 35.0, 32.2, 31.1, 16.6, 14.4. The ratio of diastereomeric ketones **38** was 1.8:1, based on integration of the methyl doublets at δ 0.89 and δ 0.95 in the ^1H NMR spectrum.

To the above 7:1 mixture of **38** and **35** (220 mg) in CH_2Cl_2 (30 mL) under Ar at rt were successively added mCPBA (665 mg, 3.85 mmol) and solid $NaHCO_3$ (323 mg, 3.85 mmol), and the resulting white suspension was stirred at rt for 2 days. The reaction mixture was diluted with CH_2Cl_2 and cooled to 0 °C. Saturated aqueous $Na_2S_2O_3$ solution was added, and the resulting white suspension was stirred for 30 min. The mixture was filtered through a pad of Celite, and the solvent was evaporated under reduced pressure. The crude residue was diluted with EtOAc and successively washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (1:2 petroleum ether/EtOAc, then 1:4 petroleum ether/EtOAc) gave an inseparable mixture of the diastereomeric lactones **39** (141 mg, 55% from **35**) as a

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white solid: mp 142−145 °C; $[\alpha]_D^{21}$ −30.5 (*c* 1.07, $CHCl_3$); IR (CH_2Cl_2) 2954, 1723, 1634, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.04−7.34 (m, 5 H), 4.78 (d, *J* = 16.4 Hz, 1 H), 4.63−4.78 (m, 1 H), 4.53 (d, *J* = 16.4 Hz, 1 H), 2.84 (ddd, *J* = 17.4, 7.1, 5.1 Hz, 1 H), 2.37−2.72 (m, 3 H), 1.58−2.22 (m, 7 H), 1.20 (d, *J* = 6.2 Hz, 3 H); δ (discernible signals for minor diastereomer) 4.37−4.52 (m, 1 H), 1.29 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 172.3, 170.8, 138.5, 128.5, 126.8, 126.2, 72.4, 60.7, 45.8, 44.8, 36.2, 31.8, 31.7, 30.6, 21.4, 16.0; δ (minor diastereomer) 173.8, 170.7, 138.6, 128.4, 126.6, 126.1, 70.9, 60.7, 45.4, 44.9, 32.3, 32.2, 31.4, 29.5, 22.5, 16.1; HRMS (FD-TOF) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{23}NO_3$ 301.1678; Found 301.1677.

The ratio of diastereomeric lactones **39** was 1.8:1, based on integration of the methyl doublets at δ 1.20 and δ 1.29 in the ^1H NMR spectrum.

(6*S*,2′*RS*)-1-Benzyl-6-(2′-hydroxypropyl)-6-(3″-hydroxypropyl)piperidin-2-one (41). The lactone **39** (133 mg, 0.44 mmol) was dissolved in THF (3 mL), and $NaBH_4$ (43 mg, 1.10 mmol) was added at rt, under Ar. The resulting white suspension was allowed to reflux (65 °C, oil bath), and MeOH (0.35 mL) was added dropwise over a period of 1 h. The mixture was stirred for an additional 1 h at 65 °C. The reaction mixture was cooled to 0 °C, and 1 M aqueous HCl was added until the gas evolution was subsided. All the volatiles were evaporated under reduced pressure, and the crude residue obtained was diluted with CH_2Cl_2. The organic layer was washed once with 10% aqueous NaOH. The aqueous layer was saturated with solid NaCl and back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (10:1 EtOAc/MeOH) afforded an inseparable diastereomeric mixture of the diols **41** (124 mg, 92%) as a colorless oil: $[\alpha]_D^{22}$ −18.7 (*c* 2.10, $CHCl_3$); IR (neat) 3573−3108, 2957, 2878, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major diastereomer) 7.14−7.28 (m, 5 H), 4.67 (d, *J* = 15.9 Hz, 1 H), 4.56 (d, *J* = 15.9 Hz, 1 H), 3.80−3.88 (m, 1 H), 3.29−3.40 (m, 2 H), 2.39−2.56 (m, 2 H), 1.98−2.18 (m, 3 H), 1.57−1.89 (m, 7 H), 1.42−1.55 (m, 1 H), 1.18−1.31 (m, 1 H), 1.07 (d, *J* = 6.1 Hz, 3 H); δ (discernible signals for minor diastereomer) 4.66 (d, *J* = 15.5 Hz, 1 H), 4.45 (d, *J* = 15.5 Hz, 1 H), 3.68−3.76 (m, 1 H), 0.83 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 172.7, 139.5, 128.2, 127.2, 126.6, 64.3, 62.6, 62.2, 47.4, 45.4, 35.0, 32.8, 31.6, 27.0, 25.9, 16.8; ^{13}C NMR ($CDCl_3$, 75 MHz) δ (minor diastereomer) 173.0, 139.2, 128.2, 127.3, 126.6, 64.3, 62.8, 62.3, 47.8, 45.0, 36.0, 32.9, 31.0, 27.1, 25.5, 17.0; HRMS (FD-TOF) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{27}NO_3$ 305.1991; Found 305.1994.

The ratio of the diastereomeric diols **41** was 1.8:1, based on integration of the methyl doublets at δ 1.07 and δ 0.83 in the ^1H NMR spectrum.

(6*S*,2′*RS*)-1-Benzyl-6-(2′-hydroxypropyl)-6-((*Z*)-pent-3″-enyl)piperidin-2-one (42). To a solution of the diol **41** (63 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) at rt were successively added TEMPO (6.6 mg, 0.04 mmol) and tetrabutylammonium chloride (15 mg, 0.05 mmol). A buffer solution (pH = 8.7) containing a mixture of 0.5 M aqueous $NaHCO_3$ and 0.05 M aqueous K_2CO_3 (1:1 v/v, 2 mL) was added to the above reaction mixture, followed by *N*-chlorosuccinimide (41 mg, 0.31 mmol). The resulting biphasic mixture was vigorously stirred for 3 h at the ambient temperature and diluted with CH_2Cl_2. The two layers were separated, and the organic layer was washed once with brine. The aqueous layer was saturated with solid NaCl and back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (1:4 petroleum ether/EtOAc, then 10:1 EtOAc/MeOH) afforded an inseparable mixture of the lactol **40** and the lactone **39** (42 mg) as a colorless oil. The starting diol **41** (21 mg, 33%) was also recovered. The mixture of lactone and the lactol was directly subjected to the Wittig olefination in the next step.

$Ph_3P^+EtBr^-$ (152 mg, 0.41 mmol) was dried under vacuum at 110 °C for 1 h and cooled to rt. The above salt was suspended in THF (2 mL), and it was cooled to 0 °C under argon. KHMDS (0.78 mL, 0.5 M in toluene) was added to the above suspension. A bright orange solution resulted, to which, after 15 min at 0 °C, was added the above mixture of lactol and lactone (42 mg) in THF (2 mL) via cannula. The reaction mixture was stirred at 0 °C for 1 h and was allowed to warm to rt for 8 h. Saturated aqueous NH_4Cl was added, and the THF was evaporated under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (Et_2O, then EtOAc) to afford an inseparable diastereomeric mixture of **42** (25.1 mg, 38% over two steps) as a colorless oil. The lactone **39** (9 mg) was also recovered: $[\alpha]_D^{23}$ +5.4 (*c* 1.15, $CHCl_3$); IR (neat) 3567−3159, 2961, 2930, 1622, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.14−7.33 (m, 5 H), 5.32−5.46 (m, 1 H), 5.08−5.22 (m, 1 H), 4.83 (d, *J* = 15.6 Hz, 0.5 H), 4.78 (d, *J* = 15.8 Hz, 0.5 H), 4.43 (d, *J* = 15.8 Hz, 0.5 H), 4.36 (d, *J* = 15.6 Hz, 0.5 H), 3.80−3.90 (m, 0.5 H), 3.68−3.78 (m, 0.5 H), 2.41−2.64 (m, 2 H), 1.49−2.24 (m, 10 H), 1.09 (d, *J* = 6.1 Hz, 1.5 H), 0.79 (d, *J* = 6.1 Hz, 1.5 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 172.9, 172.5, 139.5, 139.3, 129.3, 129.3, 128.4, 128.3, 127.4, 127.2, 126.7, 126.6, 124.4, 124.4, 64.5, 64.5, 62.9, 62.6, 47.8, 47.6, 45.4, 45.0, 39.6, 38.7, 33.0, 33.0, 31.4, 31.0, 26.0, 28.5, 21.5, 21.3, 17.1, 16.9, 12.7 (× 2); HRMS (FD-TOF) *m*/*z*: $[M]^+$ Calcd for $C_{20}H_{29}NO_2$ 315.2198; Found 315.2200.

The ratio of diastereomeric alcohols **42** was ∼1.2:1, based on the integration of the methyl doublets at δ 1.09 and δ 0.79 in the ^1H NMR spectrum.

(6*R*,2′*RS*)-1-Benzyl-6-(2′-hydroxypropyl)-6-pentylpiperidin-2-one (43). The alkenol **42** (24 mg, 0.08 mmol) was dissolved in EtOH (3 mL) and subjected to the catalytic hydrogenation (1 atm H_2, balloon) over 10% palladium on carbon (3 mg). After stirring for overnight, the mixture was filtered through a pad of Celite, and EtOH was evaporated under reduced pressure. Purification by chromatography (1:2 petroleum ether/EtOAc) afforded an inseparable diastereomeric mixture of the alcohols **43** (24 mg, 100%) as a colorless oil: $[\alpha]_D^{23}$ +8.9 (*c* 1.81, $CHCl_3$); IR (CH_2Cl_2) 3560−3120, 2958, 2931, 1634, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major diastereomer) 7.15−7.29 (m, 5 H), 4.71 (d, *J* = 15.6 Hz, 1 H), 4.40 (d, *J* = 15.6 Hz, 1 H), 3.70−3.78 (m, 1 H), 2.42−2.59 (m, 2 H), 2.09−2.18 (m, 1 H), 1.45−1.91 (m, 8 H), 1.10 (d, *J* = 6.2 Hz, 3 H), 0.95−1.27 (m, 5 H), 0.81 (t, *J* = 7.1 Hz, 3 H); δ (discernible signals for minor diastereomer) 4.75 (d, *J* = 15.8 Hz, 1 H), 4.47 (d, *J* = 15.8 Hz, 1 H), 3.80−3.88 (m, 1 H), 1.98−2.05 (m, 1 H), 0.81 (t, *J* = 7.1 Hz, 3 H), 0.81 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major diastereomer) 172.9, 139.4, 128.2, 127.4, 126.6, 64.6, 63.0, 48.0, 45.0, 40.1, 33.1, 32.1, 31.1, 25.6, 23.6, 22.5, 17.2, 13.9; δ (minor diastereomer) 172.5, 139.7, 128.3, 127.3, 126.6, 64.5, 62.7, 47.7, 45.4, 39.3, 33.0, 32.0, 31.5, 26.0, 23.5, 22.5, 17.0, 13.9. HRMS (FD-TOF) *m*/*z*: $[M]^+$ Calcd for $C_{20}H_{31}NO_2$ 317.2355; Found 317.2354.

The ratio of the diastereomeric alcohols **43** was ∼1.2:1, based on integration of the hydroxymethine proton signals at δ 3.70−3.78 and δ 3.80−3.88 in the ^1H NMR spectrum.

(*R*)-(−)-Adalinine (2). Na metal was cut into small pieces and washed three times with hexanes. To the liquid NH_3 (5 mL) at −78 °C under argon was added Na metal (24 mg, 1.0 mmol), and the resulting blue colored solution was stirred at −78 °C for 30 min. To the above solution was then added **43** (18.5 mg, 0.06 mmol) in THF (3 mL) via cannula, and the reaction mixture was stirred at −78 °C for 2.5 h. Solid NH_4Cl (28 mg) was added to the above solution at −78 °C, and the reaction temperature was allowed to gradually warm to rt, by which time all of the ammonia had evaporated. The crude residue was extracted with CH_2Cl_2 (4 × 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (10:1 EtOAc/MeOH) afforded an inseparable 1.2:1 diastereomeric mixture of the debenzylated alcohol (12.2 mg, 92%) as a colorless oil. The ratio of diastereomers was determined based on integration of the hydroxymethine proton signals at δ 4.06−4.15 and δ 3.94−4.03 in the ^1H NMR spectrum.

(6R,2′RS)-6-(2′-Hydroxypropyl)-6-pentylpiperidin-2-one. $[\alpha]_D^{23}$ +15.0 (*c* 1.21, $CHCl_3$); IR (CH_2Cl_2) 3289, 3183 (br), 2961, 2930, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major diastereomer) 7.57−7.67 (br s, 1 H), 4.25−4.33 (br s, 1 H), 4.06−4.15 (m, 1 H), 2.20−2.34 (m, 2 H), 1.50−1.82 (m, 8 H), 1.06−1.45 (m, 6 H), 1.21 (d, *J* = 6.1 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H); δ (discernible signals for

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minor diastereomer) 6.49−6.55 (br s, 1 H), 3.94−4.03 (m, 1 H), 2.78−2.90 (br s, 1 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 171.7, 64.8, 57.1, 47.1, 37.8, 32.2, 31.9, 30.6, 25.4, 24.1, 22.5, 16.9, 14.0; δ (minor diastereomer) 172.7, 64.3, 56.8, 47.6, 41.7, 32.2, 31.6, 30.9, 25.5, 23.2, 22.5, 17.1, 14.0.

To a solution of the above debenzylated alcohol (8.3 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) under Ar at rt was successively added 4-methylmorpholin N-oxide (6.5 mg, 0.05 mmol), crushed molecular sieves (10 mg, 4 Å), and tetrapropylammonium perruthenate (2.5 mg, 20 mol %). The resulting green solution was stirred at rt for 1.5 h, at which time TLC analysis showed complete conversion of the alcohol. The reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. Saturated aqueous $Na_2S_2O_3$ (1 mL) was added to the filtrate, and the mixture was stirred for 10 min. The two layers were separated, and the aqueous layer was re-extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (EtOAc, then 20:1 EtOAc/MeOH) afforded **2** (8.2 mg, 100%) as a colorless oil. The ^{1}H and ^{13}C NMR spectral data of (*R*)-adalinine was found to be in good agreement with the reported[35] data: $[\alpha]_D^{23}$ −29.8 (c 0.61, CH_2Cl_2) {lit.[35c] $[\alpha]_D^{20}$ −28.3 (c 1.6, CH_2Cl_2); lit.[35b] $[\alpha]_D^{20}$ −30.4 (c 0.8, CH_2Cl_2)}; IR (CH_2Cl_2) 3379, 3054, 2957, 2936, 1714, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.55 (br s, 1 H), 2.70 (d, J = 17.8 Hz, 1 H), 2.62 (d, J = 17.8 Hz, 1 H), 2.25−2.33 (m, 2 H), 2.13 (s, 3 H), 1.50−1.87 (m, 6 H), 1.07−1.37 (m, 6 H), 0.87 (t, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.1, 171,4, 56.2, 51.3, 39.3, 31.9, 31.9, 31.4, 31.3, 23.9, 22.5, 17.3, 13.9. HRMS (FD-TOF) m/z: $[M]^+$ Calcd for $C_{13}H_{23}NO_2$ 225.1729; Found 225.1720; HPLC: Chiralcel OD column (4.6 mm × 250 mm); 90:10 v/v hexane/*i*-PrOH; flow rate, 1.0 mL/min; λ_{max} = 220 nm; t_R (*S*-**2**) = 10.9 min and t_R (*R*-**2**) = 12.1 min; >99% *ee*. The retention times for (*R*)- and (*S*)-**2** were determined by injecting a sample of (±)-**2** for HPLC analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02582.

Copies of ^{1}H and ^{13}C NMR spectra for all products, and HPLC characterization data of compounds **29** and **2** (PDF)

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Notes

The authors declare no competing financial interest.

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