Double Ring-Closing Metathesis Reaction of Nitrogen-Containing Tetraenes: Efficient Construction of Bicyclic Alkaloid Skeletons and Synthetic Application to Four Stereoisomers of Lupinine and Their Derivatives

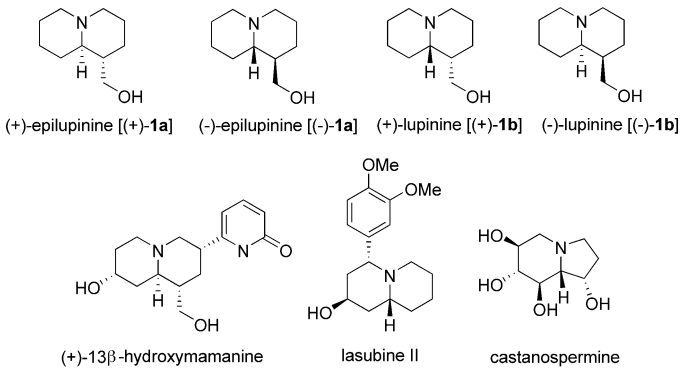
Shengming Ma* and Bukuo Ni[a]

Abstract: The double ring-closing metathesis reaction of nitrogen-containing tetraenes was studied. The selectivity of the fused/dumbbell-type products can be controlled by the electronic/steric effects of the substituents attached to the C=C bonds and the *s-cis*/*s-trans* conformational ratios of the substrates. This methodology has also been successfully applied to the enantioselective synthesis of four stereoisomers of lupinine and their derivatives.

Keywords: alkaloids · asymmetric synthesis · cyclization · heterocycles · metathesis

Introduction

A number of bicyclic alkaloids with quinolizidine and indolizidine skeletons have been isolated from a variety of natural sources in recent years. Many of these compounds have been proven to be biologically active, for example, epilupinine and lupinine (**1a** and **1b**),[1] (+)-13β-hydroxymamannine,[2] lasubine II,[3] and castanospermine[4]. Due to the varied and interesting biological activity of the fused nitrogen-containing bicyclic alkaloids, their construction has attracted much attention from synthetic organic chemists.



Indeed, many syntheses of these compounds have been reported,[5] but among the many methodologies, one of the commonly used approaches is a "ring-by-ring" strategy, which has low to moderate efficiency.[6] In addition, each synthesis is limited to the preparation of a limited range of derivatives. It would therefore be quite desirable to develop a general synthetic route to various quinolizidine and indolizidine alkaloids, and their non-natural derivatives, in order to provide candidates for screening for novel therapeutic agents.

During the past decade, the transition-metal-catalyzed ring-closing metathesis (RCM) reaction has emerged as one of the most powerful tools for the construction of cyclic compounds.[7] Recently, the use of double RCM reactions of tetraenes has been explored to provide fused,[8] spirocyclic,[9] and other bicyclic systems[10] from acyclic precursors in just "one shot".

Based on our bicyclic or tricyclic carbopalladation protocol,[11,12] our basic plan was to use a double RCM reaction, as outlined in Scheme 1, to construct the quinolizidine skeleton with Grubbs catalyst **3**[13] or **4**.[14] In order to simplify the synthetic strategy, we imagined that the double RCM reaction of nitrogen-containing acyclic tetraenes **2** might lead to the facile synthesis of bicyclic skeletons **6**, suitable for further elaboration. Here, the formidable challenge would be the control of the double RCM mode (ab/cd mode (fused-type) versus ac/bd mode (dumbbell-type), Scheme 1).

In our preliminary communication,[15] we observed that a high selectivity of cyclization mode can be realized by tuning the electronic and steric effects of the substituents attached to the C=C bonds in the nitrogen-containing tetraenes **2**. In this paper, we wish to report the scope of this double RCM reaction of tetraenes, including the factors controlling the selectivity of cyclization mode, such as the

[a] Prof. S. Ma, B. Ni
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032 (P. R. China)
Fax: (+86) 21-64167510
E-mail: masm@mail.sioc.ac.cn

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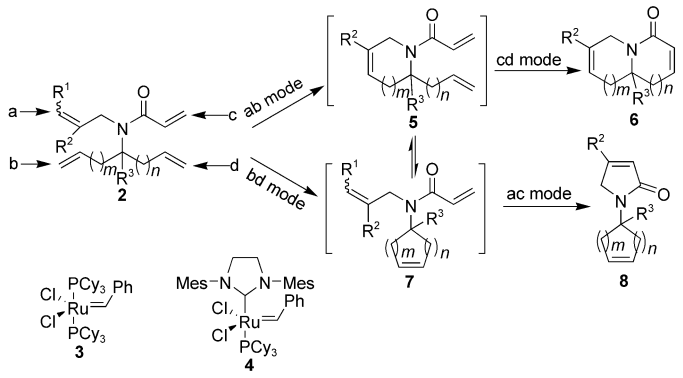
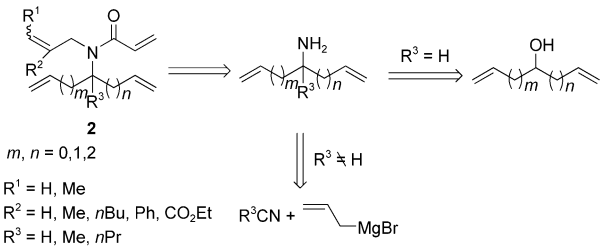


Scheme 1. Two different modes for the double RCM of tetraenes **2**. Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.

electronic, steric, and conformational factors. Finally, synthetic routes to the four stereoisomers of lupinine (see above) and their derivatives are also described.

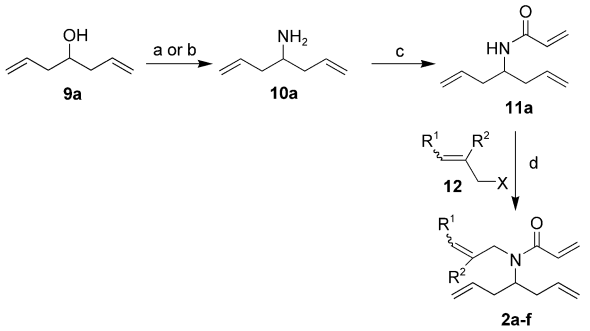
Results and Discussion

Synthesis of tetraenes: We envisioned a general approach to a variety of nitrogen-containing tetraenes **2** from α,ω-dienyl amines, which were prepared from the corresponding alcohols ($R^3 = H$) or the reaction of nitriles with allyl magnesium bromide ($R^3 \neq H$, Scheme 2).



Scheme 2. Strategy for the synthesis of **2**.

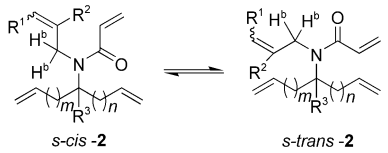
1,6-Heptadien-4-yl amine (**10a**)[16] was prepared by reduction of its azide, which was synthesized from hepta-1,6-dien-4-ol (**9a**)[17] through a Mitsunobu substitution (Scheme 3).[18a] However, this route only furnished the desired amine **10a** in low to moderate yields and the corresponding large-scale preparation of amine **10a** was not feasible. Thus, hepta-1,6-dien-4-ol (**9a**) was converted into the corresponding mesylate and this reaction was followed by substitution with sodium azide to give the corresponding azide. Subsequent reduction with $LiAlH_4$ gave amine **10a**. By this route, amine **10a** was readily prepared on a large scale with a high overall yield. Amine **10a** was then treated with a slight excess of acryloyl chloride in the presence of Et_3N to give amide **11a**, which underwent a simple allylation with allyl halides **12** to afford compounds **2a–f** (Scheme 3, Table 1).



Scheme 3. Synthesis of **2a–f**. a) 1. ZnN_6 2 Py, DIAD, PPh_3; 2. $LiAlH_4$; 50% (two steps); b) 1. MsCl, Et_3N; 2. NaN_3, HMPA; 3. $LiAlH_4$; 77% (three steps); c) CH_2=CHCOCl, Et_3N, 95%; d) NaH, DMF, RT, 58–85%. Py = pyridine, DIAD = diisopropylazodicarboxylate, Ms = mesyl = methanesulfonyl, HMPA = hexamethylphosphoramide.

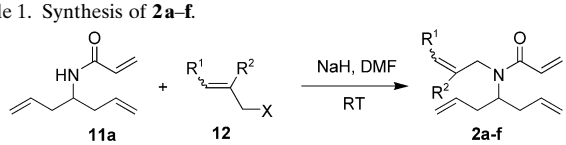
Table 1 summarizes the equilibrium ratios of two different conformers (Scheme 4), which were distinguished by their ^1H NMR spectra at room temperature based on the different chemical shift of the H^b protons in *s-cis*-**2** or *s-trans*-**2**.[19]

Alcohols **9b,c**[20] were converted into amines **10b,c** by a Mitsunobu substitution reaction (Scheme 5).[18b] Subsequent treatment of **10b,c** with acryloyl chloride gave amides **11b,c**, which were submitted to allylation to give tetraenes



Scheme 4. Two different conformers of **2**. The *cis*/*trans* nomenclature refers to the carbonyl oxygen atom and the allylic substituent.

Table 1. Synthesis of **2a–f**.



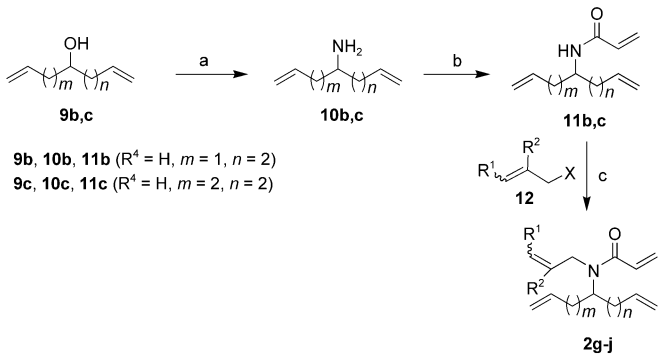
Entry	**12** (R^1, R^2, X)	*t* [h]	**2**	*s-cis*:*s-trans*	Yield [%]
1	**12a** (H, H, Br)	1.5	**2a**	33:67	85
2	**12b** (Me, H, Cl)[a]	11.5	**2b**	45:55	66
3	**12c** (H, Me, Cl)[a]	7	**2c**	21:79	67
4	**12d** (H, *n*Bu, Br)	3	**2d**	19:81	58
5	**12e** (H, Ph, Br)	8	**2e**	21:79	61
6	**12f** (H, CO_2Et, Br)	2.5	**2f**	32:68	71

[a] A catalytic amount of NaI (10 mol%) was added. See the Experimental Section for details.

Abstract in Chinese: 本文研究了含氮四烯化合物的双 RCM 反应。可以通过底物中碳碳双键上取代基的电子和立体效应以及底物的顺反构型来选择性地调控产物构型(即并环型和哑铃型)。该方法已成功地应用于 lupinine 的四个立体异构体和它们的衍生物的非对映选择性的合成中。

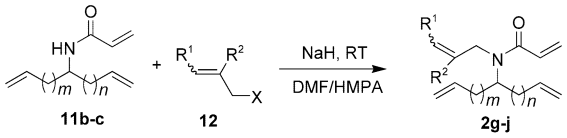
2g–j (Scheme 5) with the *s-cis*/s-*trans* ratios shown in Table 2.

For the synthesis of tetraenes **2k–n** ($R^3 \neq H$), amines **13a**,**b**[21] were treated with acryloyl chloride to afford **14aA** and **14bA**, which reacted with NaH and allyl halides **12** to



Scheme 5. Synthesis of **2g–j**. a) 1. phthalimide, DEAD, PPh_3, THF; 2. $H_2NNH_2{\cdot}H_2O$, EtOH; b) $CH_2{=}CHCOCl$, Et_3N, CH_2Cl_2; c) NaH, DMF. DEAD = diethylazodicarboxylate.

Table 2. Synthesis of **2g–j**.

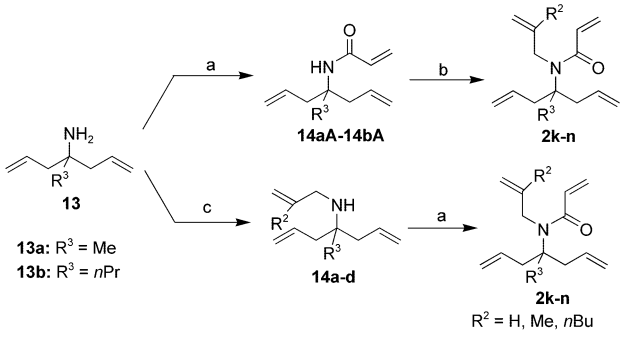


Entry	**11**	**12**	*t* [h]	**2** (R^1, R^2, R^3, *m*, *n*)	*s-cis*:*s-trans*	Yield [%]
1	**11c**	**12a**	32.5	**2g** (H, H, H, 1, 2)	37:63	62
2	**11d**	**12a**	32	**2h** (H, H, H, 2, 2)	50:50	77
3	**11d**	**12b**[a]	20.5	**2i** (Me, H, H, 2, 2)	46:54	77
4	**11d**	**12c**[a]	13	**2j** (H, Me, H, 2, 2)	28:72	45

[a] A catalytic amount of NaI (10 mol%) was added. See the Experimental Section for details.

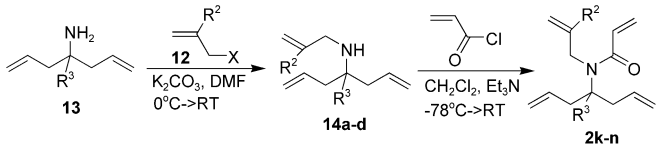
give **2k–n**. The products are in the *s-cis* conformation exclusively (Table 3), in very low yields. This low-yield problem was overcome by allylation of amines **13a**,**b** with the allyl halide first, followed by acylation with acryloyl chloride (Scheme 6).

Double RCM reaction of tetraenes for the synthesis of 6,6-fused bicyclic lactams: With the desired tetraenes **2** in hand,



Scheme 6. Synthesis of **2k–n**. a) $CH_2{=}CHCOCl$, Et_3N, CH_2Cl_2; b) NaH, **12**, DMF; c) **12**, K_2CO_3, DMF.

Table 3. Synthesis of **2k–n**.

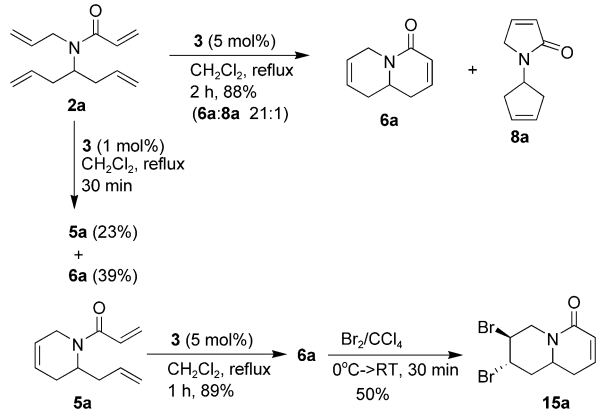


Entry	**13** (R^3)	**12**	**2** (R^2, R^3)	*s-cis*:*s-trans*	Yield [%]
1	**13a** (Me)	**12a**	**2k** (H, Me)	100:0	59
2	**13a** (Me)	**12c**[a]	**2l** (Me, Me)	100:0	62
3	**13a** (Me)	**12d**	**2m** (*n*Bu, Me)	100:0	54
4	**13b** (Pr)	**12a**	**2n** (H, *n*Pr)	100:0	62

[a] A catalytic amount of NaI (10 mol%) was added. See the Experimental Section for details.

we initiated the study of the double RCM reaction. The reaction of **2a** with **3** (5 mol%) for 2 h afforded the products with a ratio of fused-type compound **6a** versus dumbbell-type compound **8a** as high as 21:1 in a combined yield of 88% (Scheme 7). The structure of **6a** was unambiguously determined by its conversion into the *trans*-dibromide **15a**, which was characterized by an X-ray diffraction study (Figure 1).[22] It is interesting to observe that when **2a** was treated with **3** (1 mol%) for 30 min, the monocyclic intermediate **5a** was formed with high selectivity, a result suggesting that the ab mode of the RCM reaction may be much faster than the ac, bd, and cd modes; this may account for the highly selective formation of fused bicyclic product **6a**. Treatment of **5a** with **3** (5 mol%) for 1 h gave exclusively **6a** in 89% yield Scheme 7).

The reaction between triene **11a** (compared to **2a**, the 'a' C=C bond is missing) and **3** (2 mol%) gave five-membered product **16a** and six-membered product **17a** in yields of 78 and 10%, respectively (Scheme 8). No reaction was observed when **17a** was treated with **3** (5 mol%) while the reaction of **16a** with **3** (5 mol%) yielded only a trace amount



Scheme 7. RCM reaction of **2a**.

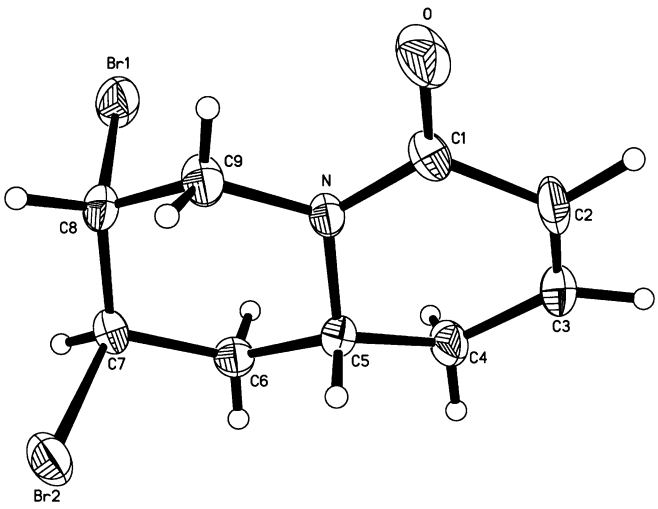
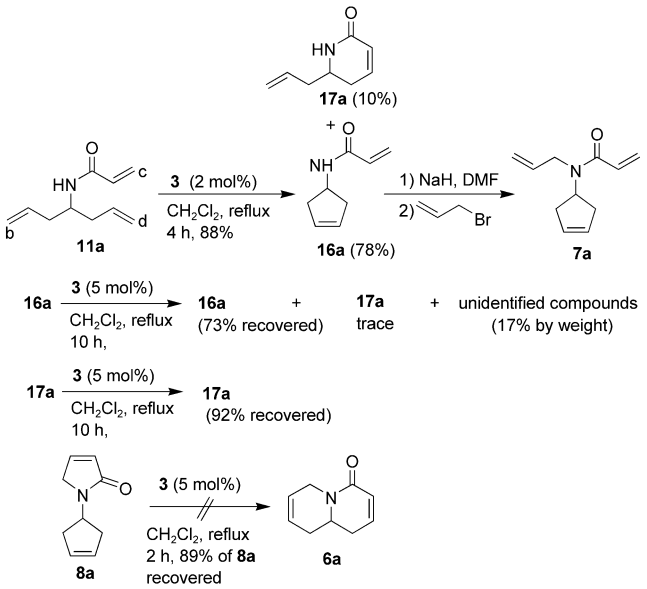


Figure 1. ORTEP representation of **15a**.

of **17a**, a fact indicating that the bd mode of the RCM reaction in **2a** is much faster than the cd mode (at least 8:1). Allylation of **16a** afforded **7a**, which was treated with **3** (5 mol%) to study the possibility of the ac mode of cyclization within **7a**. In fact, even in this case the fused bicyclic product **6a** was formed in 13% yield together with 62% of the dumbbell-type product **8a**. This result indicates that the fused bicyclic product was thermodynamically much more favorable for formation than the dumbbell-type product (Scheme 8). However, the treatment of pure dumbbell-type product **8a** with **3** under standard conditions did not give the fused-type product **6a**, a fact indicating that the interconversion between **8a** and **6a** is not possible (Scheme 8).

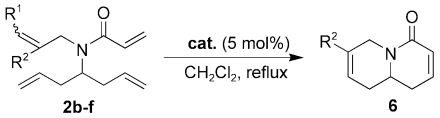
To our surprise, the reaction of **2b** (where a methyl group was introduced onto the terminal position of the 'a' C=C bond (Table 1, entry 2)) afforded fused-type **6a** as the *only* product, in 86% yield, a result that implies an interesting substituent effect on the selectivity of the cyclization



Scheme 8. RCM reactions of **11a**, **16a**, **17a**, and **8a**.

(Table 4, entry 1). In order to investigate the influence of the steric and electronic effects of the substituted C=C bonds on the reactivity and selectivity, the double RCM reaction of tetraenes **2** with the 'a' double bond substituted with alkyl, phenyl, or carbonyl groups was studied (Table 4). When tetraene **2c** was exposed to **3** (5 mol%) for 23 h, the methyl-substituted 6,6-bicyclic lactam **6c** was obtained in 43% isolated yield with no dumbbell-type products formed (Table 4, entry 2), a reaction showing high regioselectivity. Reaction of *n*-butyl substituted tetraene **2d** with **3** for 24 h gave **6d** in 38% yield together with the monocyclopentene derivative **7d** in 47% yield (Table 4, entry 4). Although the formation of these substituted fused lactams from tetraene precursors was successful with high regioselectivity, we were dissatisfied with the yields. We were pleased to find that when tetraene **2c** was exposed to the more active catalyst **4**[14] (5 mol%) for only 2 h, **6c** was formed as the single product in 90% yield (Table 4, entry 3). Some typical results with catalyst **4** are summarized in Table 4.

Table 4. Double RCM reactions of **2b–f** with **3** or **4**.

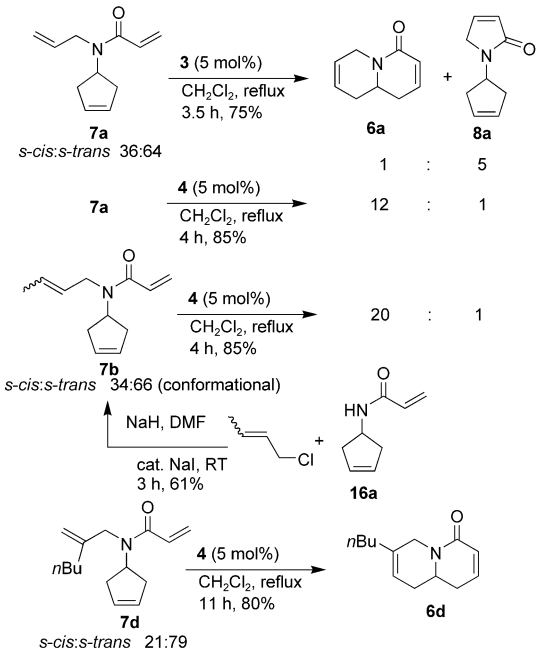


Entry	**2** (R^1, R^2)	Catalyst	*t* [h]	**6** (R^2)	Yield [%]
1	**2b** (Me, H)	**3**	5	**6a** (H)	86
2	**2c** (H, Me)	**3**	23	**6c** (Me)	43
3	**2c** (H, Me)	**4**	2	**6c** (Me)	90
4	**2d** (H, *n*Bu)	**3**	24	**6d** (*n*Bu)	38[a]
5	**2d** (H, *n*Bu)	**4**	5	**6d** (*n*Bu)	83
6	**2e** (H, Ph)	**4**	6	**6e** (H, Ph)	89
7	**2f** (H, CO_2Et)	**4**	5	**6f** (H, CO_2Et)	85

[a] **7d** (see Scheme 9) was also isolated in 47% yield.

When we subjected the monocyclic product **7d** to the standard conditions with **4** as the catalyst for 11 h, the fused bicyclic product **6d** was formed as the *only* product in 80% yield through a ring-opening/ring-closing metathesis sequence. This is different to what was observed with **7a** (Scheme 9). For the cyclization of **7a**, the different catalysts afforded **6a** and **8a** with very different ratios, a result indicating that the formation of fused bicyclic products with catalyst **4** is probably the result of thermodynamic control, while catalyst **3** may lead to the kinetically controlled products.[23] Similar improved selectivity was also observed with **7b**. The differences observed for the ROM/RCM reactions of **7a**, **7b**, and **7d** may be speculated to be caused by a combination of the steric, electronic, and conformational factors of **7**.

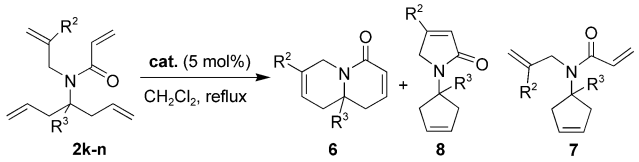
Next we turned our attention to the double RCM reaction of tetraenes **2** with $R^3 \neq H$, that is, **2k–n**. These tetraenes exist exclusively in the *s-cis* forms and, thus, may lead to the possible favorable formation of the dumbbell-type compounds **8**. The results are summarized in Table 5. As expected, the reaction of **2k** and **2n** with **3** or **4** gave a mixture of the corresponding fused bicyclic products **6k**/**6n** and dumbbell-type products **8k**/**8n** with the latter being the *major*



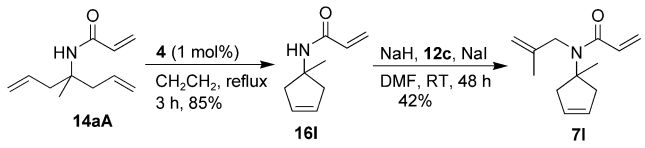
Scheme 9. RCM reactions of **7a**, **7b**, and **7d**.

product. With **3**, the monocyclic products **7k** and **7n** were also formed (Table 5, entries 1 and 3). Furthermore, it was interesting to note that with **2l** and **2m** as the starting materials and with the catalysis of **4**, the fused bicyclic products **6l** and **6m** were not formed; instead the dumbbell-type products **8l** and **8m** were isolated in very low yields with the major products being the monocyclic products of the bd mode **7l** or **7m** (Table 5, entries 5 and 6). Here, the structure of **7l** was further confirmed by comparison with an authentic sample prepared by allylation of **16l**, which was obtained from the RCM reaction of **14aA**, with **12c** (Scheme 10). The following conclusions can be drawn from these results: 1) the *s-cis* conformations and Thorpe–Ingold effect of compounds **2k–n** do favor the formation of dumbbell-type products **8**; 2) the introduction of R^2 and R^3 group greatly increases the selectivity for the formation of dumbbell-type monocyclic product **7**, probably due to the steric effect that hinders the second RCM reaction.

Table 5. Double RCM reactions of **2k–n** with **3** or **4**.

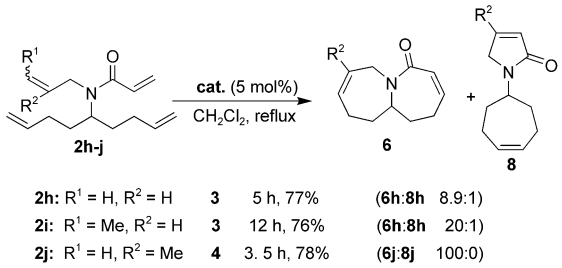


Entry	**2** (R^2, R^3)	Catalyst	*t* [h]	Yield [%] (**6**:**8**)	Yield [%] (**7**)
1	**2k** (H, Me)	**3**	16	67 (**6k**:**8k** 1:3.6)	13 (**7k**)
2	**2k** (H, Me)	**4**	5	78 (**6k**:**8k** 1:3.5)	–
3	**2n** (H, *n*Pr)	**3**	14.5	41 (**6n**:**8n** 1:3.8)	35 (**7n**)
4	**2n** (H, *n*Pr)	**4**	7	52 (**6n**:**8n** 1:2.4)	–
5	**2l** (Me, Me)	**4**	3.5	7 (**8l**)	88 (**7l**)
6	**2m** (*n*Bu, Me)	**4**	11	7 (**8m**)	90 (**7m**)



Scheme 10. Synthesis of **7l**.

Synthesis of 7,7-fused bicyclic lactams: A similar substituent effect was observed in the synthesis of 7,7-bicyclic lactams **6h–j**. Under the catalysis of **3** (5 mol%), the introduction of a methyl group to the terminal position of the 'a' C=C bond increased the selectivity of **6h**/**8h** from 8.9:1 to 20:1. Exposure of **2j** to **4** showed high selectivity and gave exclusively **6j** in 78% yield (Scheme 11).

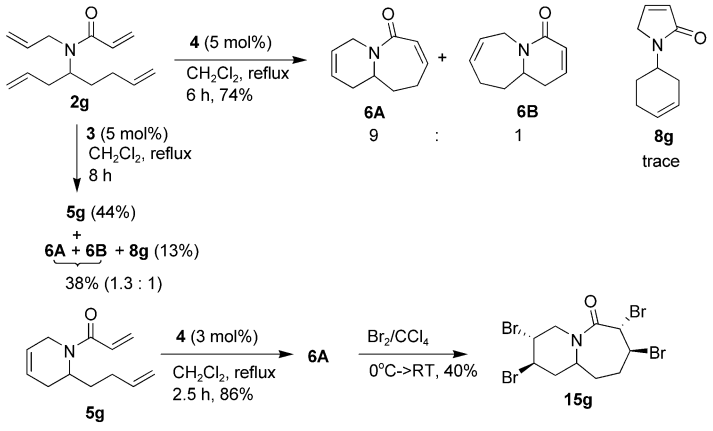


Scheme 11. Double RCM reactions of **2h–j**.

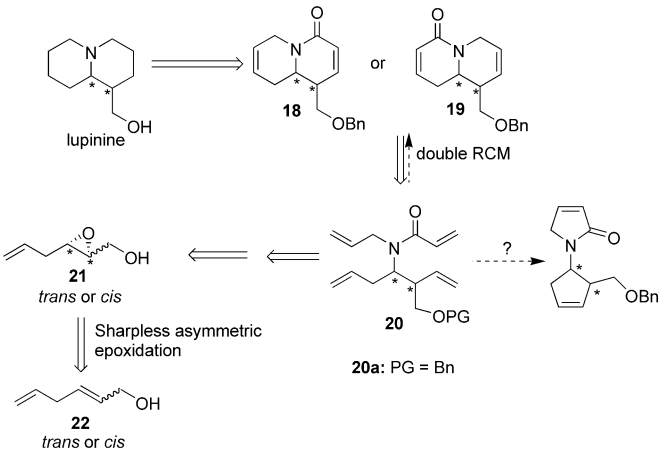
Synthesis of 6,7-fused bicyclic lactams: For the synthesis of bicyclic products with two different rings, such as 6,7-fused lactams, compound **2g** was treated with **3** (5 mol%) for 8 h to give fused lactams **6A** and **6B** in 38% combined yield as a 1.3:1 inseparable mixture, together with dumbbell-mode product **8g** in 13% yield and the monocyclic product **5g** from the the ab mode of the RCM in 44% yield (Scheme 12). However, upon treating **5g** with **4** (3 mol%) for 2.5 h, **6A** was formed exclusively in 86% yield. The structure of **6A** was unambiguously determined by its conversion into tetrabromide **15g**, which was characterized by an X-ray diffraction study (Figure 2).[24] When tetraene **2g** was exposed to **4** (5 mol%) for 6 h, a 9:1 mixture of fused bicyclic lactams **6A** and **6B** was obtained in 74% yield. It is interesting to note that under the catalysis of **4** only a trace amount of the dumbbell-type product **8g** was detected (Scheme 12).

Synthetic application to four stereoisomers of lupinine and its derivatives: Based on the above RCM results, we designed a general route for the enantioselective total synthesis of four stereoisomers of lupinine (Scheme 13). The key steps are the Sharpless asymmetric epoxidation of 2,5-hexadienol[25] and the double RCM protocol[8–10] for the construction of the fused bicyclic skeleton as discussed above.

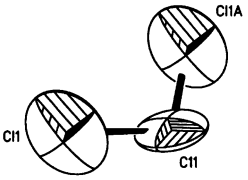
Based on the retrosynthetic analysis shown in Scheme 13, the key issues would be the preparation of the four stereoisomers of *N*-allyl-*N*-[(3-benzoxymethyl)-1,6-heptadien-4-yl] propenamide (**20a**) and the fused/dumbbell-type selectivity of the subsequent double RCM reaction. After some trial



Scheme 12. RCM reactions of **2g** and **5g**.



Scheme 13. Retrosynthetic analysis of lupinine. Bn = benzyl, PG = protecting group.



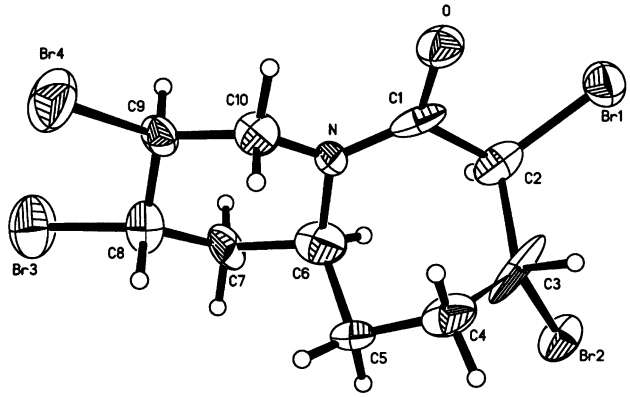


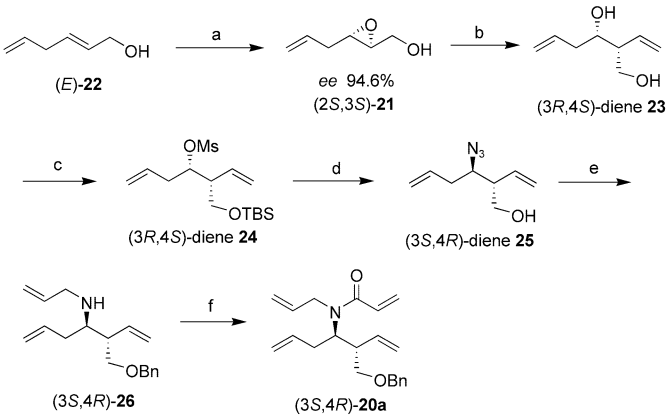
Figure 2. ORTEP representation of **15g**·CH_2Cl_2.

and error, we developed the following general synthetic route for all four stereoisomers of propenamide **20a** by using the Sharpless asymmetric epoxidation reaction[25] of (*E*)-or (*Z*)-2,5-hexadienol **22**[26] as the key step (Schemes 14 and 15).

The three-membered ring in (2*S*,3*S*)-epoxide **21** was opened by vinylation to afford (3*R*,4*S*)-diene **23**, which was converted into the corresponding protected (3*R*,4*S*)-diene **24** by regioselective protection of the primary hydroxy group followed by mesylation of the secondary hydroxy group (Scheme 14).[27] In the reaction of **24** with NaN_3, the TBS group was partially removed during the reaction, thus, TBAF was added to remove the TBS group completely and afford alcohol **25**. Benzylation of the hydroxy group followed by reduction of the azide functionality and N-allylation afforded (3*S*,4*R*)-**26**, which led to the precursor for the double RCM reaction, (3*S*,4*R*)-**20a**, upon acylation with acryloyl chloride (Scheme 14). From the results in Schemes 14 and 15, it can be seen that all four stereoisomers can be prepared in high yields and enantiopurities.

With the four stereoisomers of optically active propenamide **20a** in hand, the double RCM reactions were studied (Scheme 16). When **3** (5 mol%) was used as the catalyst, the double RCM reaction of (3*S*,4*R*)-**20a** afforded monocyclic product **27**, fused bicyclic (4*S*,5*R*)-**19**, and dumbbell-type bicyclic product **28** in 66, 13, and 7% yields, respectively; only a trace amount of the fused bicyclic product (4*S*,5*R*)-**18** was formed. However, treatment of **27** with the second generation catalyst **4** led to (4*S*,5*R*)-**18** in 91% yield (Scheme 16). Upon direct treatment of (3*S*,4*R*)-**20a** with catalyst **4**, a 1.96:1 mixture of (4*S*,5*R*)-**18** and (4*S*,5*R*)-**19** was obtained in 89% combined yield, together with 4% of the dumbbell-type cyclization product **28**, a result again demonstrating the high selectivity for the fused mode of cyclization. The structures of **18** and **19** were assigned based an NOE study of **19** (Scheme 16) and the X-ray diffraction data of **30**, a derivative of **18** (Figure 3, see Scheme 17 for structure). Finally, the two C=C bonds, the benzyl group, and carbonyl group were removed upon the treatment with Pd/C/H_2 and $LiAlH_4$, respectively, to afford (+)-**1a** (Scheme 16).

In fact this route is effective for the synthesis of all four stereoisomers of lupinine, as indicated in Table 6. The structure of the final lupinine was determined by comparison of the $^1H/^{13}C$ NMR spectroscopy data and the specific rotations with the reported data.[1k,o,p]



Scheme 14. Synthesis of (3*S*,4*R*)-**20a**. a) *t*BuOOH, MS (4 Å), L-DET, $Ti(OiPr)_4$, CH_2Cl_2, 86%; b) 1. CH_2=CHMgBr, CuI, Et_2O/THF; 2. $NaIO_4$, THF/H_2O; 69% (two steps); c) TBSCl, Et_3N, DMAP, CH_2Cl_2; 2. MsCl, Et_3N, CH_2Cl_2; 91% (two steps); d) 1. NaN_3, HMPA; 2. TBAF, THF; 97% (two steps); e) 1. NaH, BnBr, THF; 2. $LiAlH_4$, THF; 3. CH_2=$CHCH_2Br$, K_2CO_3, DMF; 75% (three steps); f) CH_2=CHCOCl, Et_3N, 90%. Ms = methanesulfonyl, L-DET = L-diethyl tartrate, TBS = *tert*-butyldimethylsilyl, DMAP = 4-dimethylaminopyridine, TBAF = tetrabutylammonium fluoride.

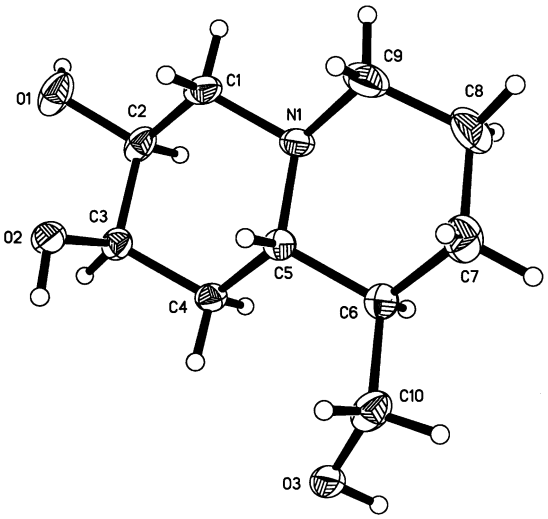
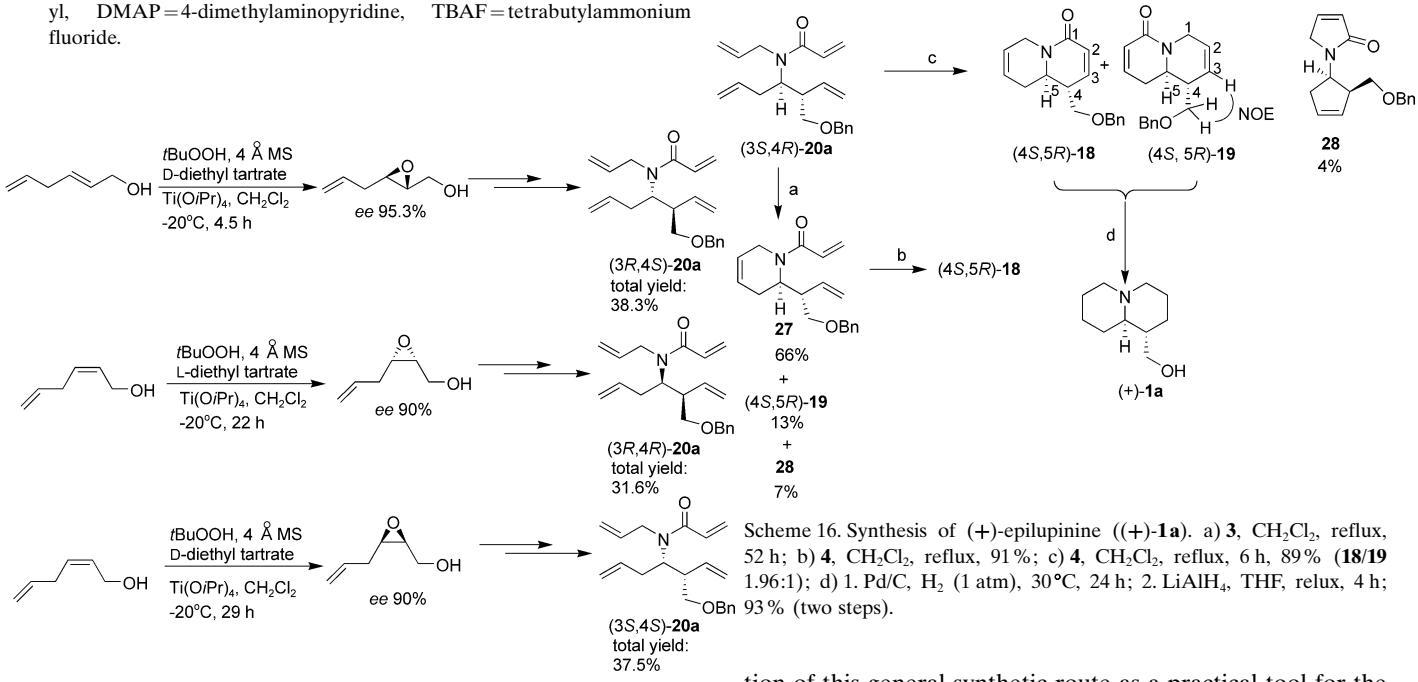


Figure 3. ORTEP representation of **30**.



Scheme 15. Synthesis of (3*R*,4*S*)-, (3*R*,4*R*)-, and (3*S*,4*S*)-**20a**.

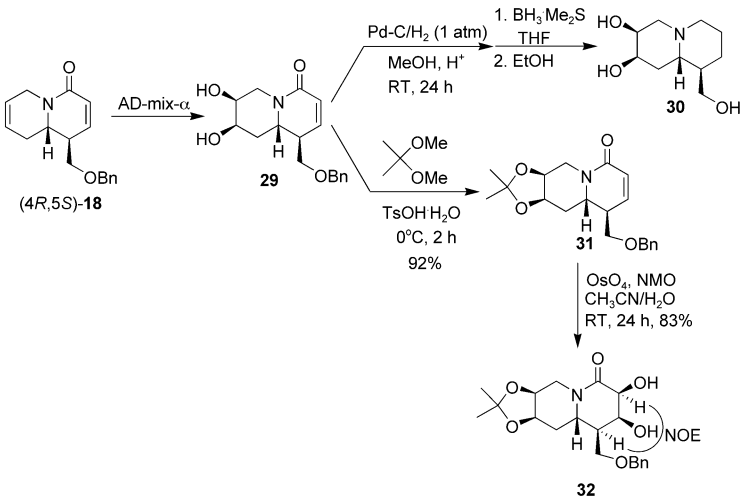
Scheme 16. Synthesis of (+)-epilupinine ((+)-**1a**). a) **3**, CH_2Cl_2, reflux, 52 h; b) **4**, CH_2Cl_2, reflux, 91%; c) **4**, CH_2Cl_2, reflux, 6 h, 89% (**18**/**19** 1.96:1); d) 1. Pd/C, H_2 (1 atm), 30 °C, 24 h; 2. $LiAlH_4$, THF, relux, 4 h; 93% (two steps).

Table 6. Synthesis of all four enantiomers of lupinine by double RCM reactions of optically active propenamides **20a** followed by reduction/deprotection.

Entry	**20a**	Yield [%] (**18**/**19**)	Yield [%] **28**		Lupinine		
					Yield [%]	*ee* [%][28]	$[\alpha]_D$
1	(3*S*,4*R*)	89 (1.96:1)	4	(+)-**1a**	95	92.7	+32.6
2	(3*R*,4*S*)	90 (2.04:1)	3	(−)-**1a**	94	91.8	−33.0
3	(3*R*,4*R*)	88 (1:1.61)	6	(−)-**1b**	93	86.5	−21.0
4	(3*S*,4*S*)	87 (1:1.59)	6	(+)-**1b**	93	85.9	+20.8

It is obvious that the current approach used to construct the four stereoisomers of lupinine might also be applicable to other related quinolizidine alkaloids and their analogues. Functionalization of **18** and **19** would allow further evaluation of this general synthetic route as a practical tool for the synthesis of polyoxygenated quinolizidine derivatives.

Thus, as an typical example, fused bicyclic product (4*R*,5*S*)-**18** was dihydroxylated with AD mix α, with the osmium reagent attacking the electron-rich C=C bond from the β side, to afford the desired product **29** in 82% yield (Scheme 17). Bicyclic lactam **29** was subsequently converted into **30** through hydrogenation of the electron-deficient C=C bond and reduction of the carbonyl group in a good overall yield. The stereochemistry of **30** was unambiguously established by an X-ray diffraction study (Figure 3).[29] Protection of the diol in **29** as an acetal functionality afforded **31** in 92%



Scheme 17. Transformation of (4*R*,5*S*)-**18**. AD = asymmetric dihydroxylation, Ts = tosyl = toluene-4-sulfonyl, NMO = 4-methylmorpholine *N*-oxide.

yield. Subsequent dihydroxylation of the electron-deficient C=C bond in **31** was accomplished by treatment with OsO_4 and NMO in CH_3CN/H_2O at room temperature for 24 h, to give **32** in 83% yield as a single isomer. An NOE study on

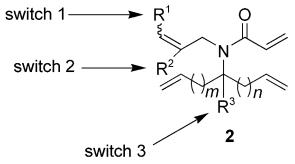


Figure 4. Switches in tetraenes **2** for controlling the selectivity of their double RCM reaction.

32 indicated that dihydroxylation of the double bond occurred from the β side (Scheme 17). The polyoxygenated quinolizidine derivative **32** should be a useful intermediate for the synthesis of a variety of polyhydroxy quinolizidines.

Conclusion

In the double RCM reaction of nitrogen-containing tetraenes **2**, interesting steric and electronic effects of the substituents of the C=C bond in **2** and conformational effects of the tetraenes **2** were observed to lead to a highly selective synthesis of the quinolizidine alkaloid skeleton. The effects (Figure 4) were as follows: 1) introduction of substituents onto the 'a' C=C bond increases the ab/cd versus ac/bd selectivity (Scheme 1); 2) introduction of an alkyl group R^3 (R^3 = Me or *n*Pr, Scheme 1) makes the starting amides **2** display the *s-cis* conformation exclusively, thereby increasing the possibility of the bd/ac mode of the RCM reaction and leading to the dumbbell-type products **8**.

The selectivity also depends on the ruthenium catalyst used: **4** favors the formation of fused bicyclic products and shows a higher activity and selectivity.

A general enantioselective methodology for the total synthesis of four stereoisomers of lupinine has been developed by using the Sharpless enantioselective epoxidation and the double RCM reaction as the key steps. Compared to the known methods, the current method enjoys high stereoselectivity, high yields, and generality for all four stereoisomers of lupinine. Due to the diversity of the easily available starting materials, this methodology can also be applied to the synthesis of analogues of quinolizidine alkaloids.

Experimental Section

Preparation of the starting compounds: Allyl bromide (**12a**), crotyl chloride (**12b**), and 3-chloro-2-methylpropene (**12c**) were commercially available. 3-Bromo-2-butylpropene (**12d**),[30] 3-bromo-2-phenylpropene (**12e**),[31] and 2-bromomethyl acrylic acid ethyl ester (**12f**)[32] were prepared according to the reported procedures.

Synthesis of tetraenes

Synthesis of 10a: Methanesulfonyl chloride (4.17 g, 36.43 mmol) was added to a solution of **9a**[18] (3.40 g, 30.36 mmol) and Et_3N (5.5 mL, 45.54 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C. After warming to RT, the reaction mixture was stirred for 2 h, quenched with H_2O, and extracted with CH_2Cl_2. The combined extracts were washed with brine and dried over $MgSO_4$. Evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate 15:1) gave the corresponding mesylate (4.95 g, 86%) as a colorless oil, which was used for the next step without further characterization.

A mixture of the mesylate (4.80 g, 25.26 mmol) and NaN_3 (3.28 g, 50.52 mmol) in anhydrous HMPA (8 mL) was heated at 40 °C for 4 h with stirring. The reaction mixture was then poured into water (30 mL) and extracted with Et_2O. The combined organic solutions were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed by distillation under atmospheric pressure to afford the crude azide, which was used for the next step directly.

The crude azide in THF (20 mL) was added slowly to a suspension of $LiAlH_4$ (1.92 g, 50.53 mmol) in THF (100 mL) through an addition funnel. After the addition, the reaction mixture was stirred at RT for 8 h and quenched by careful addition of water (4 mL) with cooling (dry ice/acetone bath). The reaction mixture was then warmed to RT and filtered. The solvent was removed and the residue was distilled to give **10a**[17] (2.52 g, 77% for three steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85–5.70 (m, 2H), 5.15–5.03 (m, 4H), 2.90–2.75 (m, 1H), 2.25–2.18 (m, 2H), 1.18–1.95 (m, 2H), 1.60–1.30 (brs, 2H) ppm.

Synthesis of 11a: CH_2=CHCOCl (3.17 g, 35.14 mmol) in diethyl ether (10 mL) was added to a solution of 1,6-heptadien-4-yl amine (**10a**, 3.00 g, 27.03 mmol) and Et_3N (4.89 mL, 35.14 mmol) in Et_2O (100 mL) at −78 °C. After the addition, the reaction mixture was warmed to RT, quenched with water, and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) gave **11a** (4.23 g, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.17 (dd, J = 16.5, 1.2 Hz, 1H), 6.00 (dd, J = 17.1, 10.4 Hz, 1H), 5.90–5.40 (m, 4H), 5.10–4.80 (m, 4H), 4.20–3.97 (m, 1H), 2.40–2.05 (m, 4H) ppm; IR (neat): $\tilde{\nu}$ = 3225, 1656, 1632 cm^{-1}; MS (EI): *m*/*z* (%): 166 [M^++H] (20.4), 124 [M^+−C_3H_5] (60.7), 70 (100.0); HRMS (EI): *m*/*z*: calcd for $C_7H_{10}NO$ [M^+−C_3H_5]: 124.07624; found: 124.07664.

General procedure A—Synthesis of 2a: Compound **11a** (400 mg, 2.42 mmol) in DMF (6 mL) was added to a suspension of NaH (94 mg, 80% in paraffin oil, 3.15 mmol) in DMF (2 mL). After the addition, the mixture was stirred for additional 15 min at RT. Then, allyl bromide (**12a**, 590 mg, 4.84 mmol) was added dropwise at RT. After the mixture was stirred at RT for 1 h, the reaction was quenched with water and extracted with diethyl ether. The combined organic extracts were washed with brine and dried over $MgSO_4$, then the solvent was evaporated. The crude product was further purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give **2a** (421 mg, 85%) as

a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.65–6.15 (m, 2H), 6.00–5.60 (m, 4H), 5.25–4.96 (m, 6H), 4.83–4.68 (m, 0.7H), 4.06–3.94 (m, 0.3H), 3.94–3.86 (m, 0.6H), 3.86–3.77 (m, 1.4H), 2.40–2.20 (m, 4H) ppm; IR (neat): $\tilde{\nu}$ = 3078, 1650, 1612, 1425 cm^{-1}; MS (EI): *m*/*z* (%): 206 [M^++H] (36.8), 110 (100.0); elemental analysis calcd for $C_{13}H_{19}NO$: C 76.06, H 9.33, N 6.82; found: C 75.90, H 9.24, N 7.12.

General procedure B—Synthesis of 2b: Compound **11a** (250 mg, 1.52 mmol) in DMF (2 mL) was added to a suspension of NaH (70 mg, 80% in paraffin oil, 2.28 mmol) in DMF (2 mL). After the addition, the mixture was stirred for an additional 15 min at RT, NaI (23 mg, 10 mol%) and **12b** (274 mg, 3.04 mmol) were subsequently added at RT. After the mixture was stirred at RT for 11.5 h, the reaction was quenched with water and extracted with diethyl ether. The combined organic extracts were washed with brine and dried over $MgSO_4$, then the solvent was evaporated. The crude product was further purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give **2b** (220 mg, 66%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.64–6.16 (m, 2H), 5.84–5.30 (m, 5H), 5.20–4.90 (m, 4H), 4.86–4.70 (m, 0.5H), 4.06–3.90 (m, 0.5H), 3.90–3.82 (m, 1H), 3.82–3.68 (m, 1H), 2.46–2.18 (m, 4H), 1.76–1.60 (m, 3H) ppm; IR (neat): $\tilde{\nu}$ = 2918, 1645, 1612 cm^{-1}; MS (EI): *m*/*z* (%): 178 [$M^+-C_3H_5$] (67.1), 124 (100.00); elemental analysis calcd for $C_{14}H_{21}NO$: C 76.67, H 9.65, N 6.39; found: C 76.39, H 9.55, N 6.66.

Synthesis of 10b: DEAD (12.84 g, 40% in toluene, 29.52 mmol) was added to a solution of **9b**[21a] (3.10 g, 24.60 mmol), PPh_3 (7.09 g, 27.06 mmol), and phthalimide (3.98 g, 27.06 mmol) in THF (170 mL) through an addition funnel. The resulting solution was stirred at RT for 13 h. The solvent was then evaporated to afford the semisolid material, which was taken up in petroleum ether/diethyl ether 2:1. The resulting precipitate was washed with several portions of petroleum ether/diethyl ether 2:1. Evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate 20:1) gave the corresponding phthalimide (4.31 g, 69%) as a colorless oil, which was used for the next step without further characterization.

A solution of the phthalimide (4.31 g, 16.89 mmol) and hydrazine hydrate (1.7 mL, 35.02 mmol) in absolute EtOH (150 mL) was heated to reflux for 6 h; this resulted in the formation of a white precipitate. The reaction mixture was cooled to RT and quenched with HCl (20 mL). The precipitate was removed by filtration and the filtrate was concentrated. The residue was adjusted to pH > 10 by the addition of 9N aq. NaOH solution. The solution was extracted with diethyl ether (4 × 100 mL) and washed with brine, then the combined extracts were dried over $MgSO_4$, filtered, and concentrated to afford the crude amine **10b** (2.57 g), which was used for the next step without further purification.

Synthesis of 11b: CH_2=CHCOCl (434 mg, 4.80 mmol) was added to a solution of crude **10b** (500 mg, 4.00 mmol) and Et_3N (0.73 mL, 6.00 mmol) in CH_2Cl_2 (6 mL) at −78°C. After the addition, the reaction mixture was warmed to RT, quenched with water, and extracted with diethyl ether. The combined extracts were washed with brine and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) gave **11b** (509 mg, 71%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.50–6.00 (m, 2H), 5.94–5.38 (m, 4H), 5.15–4.90 (m, 4H), 4.20–4.03 (m, 1H), 2.40–2.20 (m, 2H), 2.20–2.18 (m, 2H), 1.70–1.45 (m, 2H) ppm; IR (neat): $\tilde{\nu}$ = 3275, 1656, 1627, 1549 cm^{-1}; MS (ESI): *m*/*z*: 180.2 [M^++H]; HRMS (ESI): *m*/*z*: calcd for $C_{11}H_{17}NONa$: 202.12079; found: 202.12064.

General procedure C—Synthesis of 2g: Compound **11b** (500 mg, 2.793 mmol) was added to a suspension of NaH (85 mg, 95% in paraffin oil, 3.352 mmol) in DMF (4 mL). After the addition, the mixture was stirred for additional 30 min at RT and this was followed by the addition of **12a** (676 mg, 5.586 mmol) and HMPA (1 mL) at RT. After the mixture was stirred at RT for 32 h, the reaction was quenched with water and extracted with diethyl ether. The combined organic extracts were washed with brine and dried over $MgSO_4$, then the solvent was evaporated. The crude product was further purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give **2g** (379 mg, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60–6.20 (m, 2H), 6.06–5.55 (m, 4H), 5.40–4.90 (m, 6H), 4.85–4.60 (m, 0.6H), 4.10–3.70 (m, 2.4H), 2.50–2.20 (m, 2H), 2.20–1.98 (m, 2H), 1.80–1.50 (m, 2H) ppm; IR (neat): $\tilde{\nu}$ = 2928, 1640, 1613, 1425 cm^{-1}; MS (ESI): *m*/*z*: 220.1 [M^++H]; HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{21}NONa$: 242.15209; found: 242.15145.

General procedure D—Synthesis of 2i: Compound **11c** (300 mg, 1.55 mmol) was added to a suspension of NaH (140 mg, 80% in paraffin oil, 4.65 mmol) in DMF (4 mL). After the addition, the mixture was stirred for additional 30 min at RT and this was followed by the sequential addition of NaI (23 mg, 10 mol%), **12b** (420 mg, 4.65 mmol), and HMPA (1 mL) at RT. After the mixture was stirred at room temperature for 20 h, the reaction was quenched with water and extracted with diethyl ether. The combined organic extracts were washed with brine and dried over $MgSO_4$, then the solvent was evaporated. The crude product was further purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give **2i** (294 mg, 77%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.64–6.20 (m, 2H), 5.90–5.30 (m, 5H), 5.10–4.80 (m, 4H), 4.78–4.50 (m, 0.5H), 4.00–3.60 (m, 2.5H), 2.20–1.40 (m, 11H) ppm; IR (neat) $\tilde{\nu}$ = 2931, 1644, 1612, 1425 cm^{-1}; MS (ESI): *m*/*z*: 248.2 [M^++H]; HRMS (ESI): *m*/*z*: calcd for $C_{16}H_{25}NONa$: 270.18339; found: 270.18348.

General procedure E—Synthesis of 2k: Allyl bromide (**12a**, 425 mg, 3.36 mmol) was added to a solution of **13a** (400 mg, 3.20 mmol) and K_2CO_3 (883 mg, 6.40 mmol) in DMF (5 mL) at 0°C. After the addition, the reaction mixture was stirred for 1 h at 0°C and then warmed to RT. After stirring for 4 h, the reaction mixture was quenched with water (5 mL) and extracted with diethyl ether. The combined extracts were washed with brine and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleun ether/ethyl acetate 8:1 with a small amount of Et_3N) gave **14a** (370 mg) as a colorless oil, which was used for the next step directly.

CH_2=CHCOCl (244 mg, 2.69 mmol) was added to a solution of **14a** (370 mg, 2.24 mmol) and Et_3N (0.47 mL, 3.36 mmol) in CH_2Cl_2 (8 mL) at −78°C. After the addition, the reaction mixture was warmed to RT, quenched with water, and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether/ethyl acetate 8:1) gave **2k** (416 mg, two steps: 59%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.40 (dd, *J* = 16.4, 10.3 Hz, 1H), 6.17 (dd, *J* = 16.7, 2.2 Hz, 1H), 5.80–5.60 (m, 3H), 5.50 (dd, *J* = 10.3, 2.2 Hz, 1H), 5.25–4.88 (m, 6H), 3.88–3.75 (m, 2H), 3.13 (dd, *J* = 13.4, 7.3 Hz, 2H), 2.27 (dd, *J* = 13.4, 7.6 Hz, 2H), 1.23 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3, 136.2, 134.5, 131.6, 126.8, 118.3, 116.5, 62.7, 48.5, 42.6, 23.6 ppm; IR (neat): $\tilde{\nu}$ = 1655, 1615 cm^{-1}; MS (EI): *m*/*z* (%): 178 [$M^+-C_3H_5$] (52.9), 124 (100.0); elemental analysis calcd for $C_{14}H_{21}NO$: C 76.67, H 9.65, N 6.39; found: C 76.56, H 9.69, N 6.04.

Double RCM reaction of 2a

General procedure F—Preparation of 6a and 8a: The Grubbs catalyst (**3**, 38 mg, 5 mol%) was added to a solution of **2a** (175 mg, 0.854 mmol) in CH_2Cl_2 (29 mL) under an Ar atmosphere. After being stirred under reflux conditions for 2 h, the resulting solution was concentrated and purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 3:1) to give **6a** (107 mg, 84%) as a colorless oil and **8a** (5 mg, 4%) as a colorless oil. **6a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.44 (dt, *J* = 9.7, 4.4 Hz, 1H), 5.89 (dt, *J* = 9.7, 1.7 Hz, 1H), 5.83–5.65 (m, 2H), 4.75–4.55 (m, 1H), 3.85–3.70 (m, 1H), 3.65–3.50 (m, 1H), 2.75–2.60 (m, 2H), 2.50–2.15 (m, 2H), 2.10–1.90 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8, 137.1, 124.4, 124.2, 124.1, 50.8, 42.1, 31.0, 28.9 ppm; IR (neat): $\tilde{\nu}$ = 3414, 1627, 1568 cm^{-1}; MS (EI): *m*/*z* (%): 150 [M^++H] (100.0), 149 [M^+] (45.5); HRMS (EI): *m*/*z*: calcd for $C_9H_{11}NO$: 149.08407; found: 149.08580. **8a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01 (dt, *J* = 6.1, 1.8 Hz, 1H), 6.07 (dt, *J* = 6.1, 1.8 Hz, 1H), 5.71 (s, 2H), 5.05–4.85 (m, 1H), 3.85–3.80 (m, 2H), 2.67 (dd, *J* = 15.4, 8.6 Hz, 2H), 2.20 (dd, *J* = 15.4, 3.7 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 142.5, 129.2, 127.9, 49.4, 49.2, 38.9, 38.1 ppm; IR (neat): $\tilde{\nu}$ = 3410, 1630, 1547 cm^{-1}; MS (EI): *m*/*z* (%): 149 [M^+] (5.6), 84 (100.0); HRMS (EI): *m*/*z*: calcd for $C_9H_{11}NO$: 149.08407; found: 149.08300.

Preparation of 5a and 6a: Following GP F, a solution of **2a** (175 mg, 0.854 mmol) and **3** (8 mg, 1 mol%) in CH_2Cl_2 (18 mL) was stirred under reflux for 0.5 h to afford **5a** as a liquid (34 mg, 23%) and **6a** (49 mg, 39%). **5a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = [6.52 (dd, *J* = 16.8, 10.4 Hz), 6.45 (dd, *J* = 16.8, 10.4 Hz), 1H], [6.20 (dd, *J* = 16.8, 1.8 Hz), 6.17 (dd, *J* = 16.8, 1.8 Hz), 1H], 5.84–5.44 (m, 4H), 5.16–4.80 (m, 2.5H), 4.01 (AA′BB′,

$\Delta\nu$ = 359.83 Hz, J = 18.6 Hz, 1H), 4.24–4.00 (m, 1H), 3.80–3.62 (m, 0.5H), 2.50–1.80 (m, 4H) ppm; IR (neat): $\tilde{\nu}$ = 3394, 2888, 1597, 1569, 1312, 1248, 1158, 1126, 963 cm^{-1}; MS (EI): m/z (%): 177 [M^+] (1.8), 82 (100.0); HRMS (EI): m/z: calcd for $C_{11}H_{15}NO$: 177.11536; found: 177.11589.

General procedure G—Bromination of 6a: A solution of **6a** (30 mg, 0.2 mmol) in CCl_4 (1 mL) was treated with a solution of bromine (0.03875 M, 5.2 mL, 0.2 mmol) in CCl_4 at 0 °C by slow addition. When the addition was complete, the reaction was warmed to RT with stirring for 30 min, concentrated, and purified by flash column chromatography on silica gel (petroleum ether/diethyl ether 2:3) to give **15a** (31 mg, 50%) as a white solid. M.p. 96–97 °C (recrystallized from dichloromethane/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.55 (dt, J = 10.4, 3.1 Hz, 1H), 5.97 (dt, J = 10.4, 1.8 Hz, 1H), 4.75 (d, J = 15.9 Hz, 1H), 4.70–4.54 (m, 2H), 4.10–3.90 (m, 1H), 3.63 (dd, J = 15.8, 2.4 Hz, 1H), 2.84–2.70 (m, 1H), 2.70–2.60 (m, 1H), 2.40–2.30 (m, 1H), 2.10–1.90 (m, 1H) ppm; IR (KBr): $\tilde{\nu}$ = 2848, 1668, 1616, 1427, 1343, 1320, 1275, 1144, 1067, 815 cm^{-1}; MS (EI): m/z (%): 311 [M^+] with 2×^{81}Br (1.7), 309 [M^+] with 1×^{81}Br, 1×^{79}Br (3.6), 307 [M^+] with 2×^{79}Br (2.4), 228 (100.0); elemental analysis calcd for $C_9H_{11}NOBr_2$: C 34.98, H 3.59, N 4.53; found: C 35.12, H 3.59, N 4.42.

RCM reaction of 11a

Preparation of 16a and 17a: Following GP F, a solution of **11a** (350 mg, 2.121 mmol) and **3** (37 mg, 2 mol%) in CH_2Cl_2 (25 mL) was stirred under reflux conditions for 4 h to afford **16a** (227 mg, 78%) and **17a** (30 mg, 10%). **16a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.28 (dd, J = 17.1, 1.5 Hz, 1H), 6.05 (dd, J = 16.9, 10.3 Hz, 1H), 5.90–5.70 (m, 3H), 5.63 (dd, J = 10.2, 1.5 Hz, 1H), 4.73–4.58 (m, 1H), 2.80 (dd, J = 15.2, 7.6 Hz, 2H), 2.23 (dd, J = 15.1, 3.7 Hz, 2H) ppm; IR (neat): $\tilde{\nu}$ = 3249, 1653, 1620, 1557, 1253, 1072 cm^{-1}; MS (EI): m/z (%): 138 [M^++H] (33.5), 55 (100.0); elemental analysis calcd for $C_8H_{11}NO$: C 70.04, H 8.08, N 10.21; found: C 69.66, H 8.00, N 10.13. **17a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.60–6.50 (m, 1H), 5.85 (d, J = 9.8 Hz, 1H), 5.75–5.50 (m, 2H), 5.17–5.12 (m, 2H), 3.65–3.50 (m, 1H), 2.40–2.05 (m, 4H) ppm; IR (neat): $\tilde{\nu}$ = 3225, 2932, 1681, 1612 cm^{-1}; MS (ESI): m/z: 138.1 [M^++H].

Synthesis and RCM reaction of monocyclic compounds 7a and 7b

Synthesis of 7a: Following GP A, a solution of **16a** (80 mg, 0.577 mmol) in DMF (2 mL) was treated sequentially with NaH (21 mg, 80% in paraffin oil, 0.692 mmol, 30 min) and **12a** (140 mg, 1.154 mmol, 1 h) to give **7a** (93 mg, 90%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.70–6.20 (m, 2H), 6.00–5.60 (m, 4H), 5.50–5.30 (m, 0.64H), 5.30–5.00 (m, 2H), 4.80–4.64 (m, 0.36H), 4.05–3.80 (m, 2H), 2.78–2.68 (m, 2H), 2.52–2.22 (m, 2H) ppm; IR (neat): $\tilde{\nu}$ = 1651, 1614 cm^{-1}; MS (EI): m/z (%): 178 [M^++H] (7.0), 177 [M^+] (8.0), 55 (100.0); HRMS (EI): m/z: calcd for $C_{11}H_{15}NO$: 177.11536; found: 177.11429.

RCM reaction of 7a with 3 as the catalyst: Following GP F, a solution of **7a** (90 mg, 0.508 mmol) and **3** (23 mg, 5 mol%) in CH_2Cl_2 (5 mL) was stirred under reflux conditions for 3.5 h to afford **6a** and **8a** (combined yield: 57 mg, 75%) in a ratio of 1:5 as a colorless oil.

RCM reaction of 7a with 4 as the catalyst: Following GP F, a solution of **7a** (66 mg, 0.373 mmol) and **4** (16 mg, 5 mol%) in CH_2Cl_2 (8 mL) was stirred under reflux conditions for 4 h to afford **6a** and **8a** (combined yield: 47 mg, 85%) in a ratio of 12:1 as a colorless oil.

Synthesis of 7b: Following GP B, a solution of **16a** (200 mg, 1.460 mmol) in DMF (4 mL) was treated sequentially with NaH (70 mg, 60% in paraffin oil, 1.752 mmol, 30 min), NaI (22 mg, 10 mol%), and **12b** (198 mg, 2.190 mmol, 3 h) to give **7b** (171 mg, 61%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.70–6.20 (m, 2H), 5.78–5.22 (m, 5H), 4.80–4.60 (m, 0.34H), 4.00–3.70 (m, 2.66H), 2.75–2.55 (m, 2H), 2.55–2.20 (m, 2H), 1.75–1.55 (m, 3H) ppm; IR (neat): $\tilde{\nu}$ = 2918, 1650, 1611, 1428 cm^{-1}; MS (ESI): m/z: 192.2 [M^++H]; HRMS (ESI): m/z: calcd for $C_{12}H_{18}NO$: 192.13884; found: 192.13753.

RCM reaction of 7b with 4 as the catalyst: Following GP F, a solution of **7b** (75 mg, 0.393 mmol) and **4** (17 mg, 5 mol%) in CH_2Cl_2 (8 mL) was stirred under reflux conditions for 4 h to afford **6a** and **8a** (combined yield: 53 mg, 91%) in a ratio of 20:1 as a colorless oil.

RCM reaction of 2c

Preparation of 6c: Following GP F, a solution of **2c** (42 mg, 0.192 mmol) and **4** (8 mg, 5 mol%) in CH_2Cl_2 (4 mL) was stirred under reflux conditions for 2 h to afford **6c** (28 mg, 90%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.36 (dt, J = 9.8, 4.3 Hz, 1H), 5.80 (dt, J = 9.8, 1.8 Hz, 1H), 5.41–5.33 (m, 1H), 4.39 (d, J = 17.7 Hz, 1H), 3.66–3.54 (m, 1H), 3.39 (d, J = 18.3 Hz, 1H), 2.65–2.50 (m, 1H), 2.42–2.07 (m, 1H), 1.98–1.84 (m, 2H), 1.60 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3, 137.4, 131.9, 124.5, 118.7, 50.9, 46.0, 31.5, 29.3, 20.5 ppm; IR (neat): $\tilde{\nu}$ = 2915, 2838, 1678, 1644, 1612, 1431, 1255, 803 cm^{-1}; MS (EI): m/z (%): 164 [M^++H] (73.3), 163 [M^+] (100.0); HRMS (EI): calcd for $C_9H_{11}NO$: 163.09971; found: 163.09988.

RCM reaction of 2d

Preparation of 6d and 7d: Following GP F, a solution of **2d** (120 mg, 0.460 mmol) and **3** (20 mg, 5 mol%) in CH_2Cl_2 (18 mL) was stirred under reflux conditions for 24 h to afford **6d** (36 mg, 38%) as a colorless oil and **7d** (50 mg, 47%) as a colorless oil. **7d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.67–6.23 (m, 2H), 6.00–5.57 (m, 3H), 5.37–5.25 (m, 0.8H), 4.97 (s, 1H), 4.84 (s, 1H), 4.75–4.60 (m, 0.2H), 3.89 (s, 0.4H), 3.73 (s, 1.6H), 2.64 (dd, J = 15.1, 9.3 Hz, 2H), 2.50–2.20 (m, 2H), 2.01 (t, J = 7.5 Hz, 2H), 1.50–1.20 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H) ppm; IR (neat): $\tilde{\nu}$ = 2930, 1655, 1613, 1424 cm^{-1}; MS (ESI): m/z (%): 234.2 [M^++H]; HRMS (ESI): m/z: calcd for $C_{15}H_{23}NONa$: 256.16774; found: 256.16774.

RCM reaction of 7d with 4 as the catalyst: Following GP F, a solution of **7d** (77 mg, 0.330 mmol) and **4** (14 mg, 5 mol%) in CH_2Cl_2 (7 mL) was stirred under reflux conditions for 11 h to afford **6d** (54 mg, 80%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.41 (dt, J = 9.7, 4.2 Hz, 1H), 5.86 (dt, J = 9.8, 2.1 Hz, 1H), 5.47–5.39 (m, 1H), 4.46 (d, J = 18.2 Hz, 1H), 3.71–3.58 (m, 1H), 3.48 (br d, J = 17.9 Hz, 1H), 2.70–2.52 (m, 1H), 2.38–2.10 (m, 2H), 2.07–1.90 (m, 3H), 1.44–1.18 (m, 4H), 0.86 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 137.4, 136.4, 124.9, 118.1, 51.3, 45.2, 34.7, 31.8, 30.0, 29.6, 22.6, 14.1 ppm; IR (neat) $\tilde{\nu}$ = 3456, 2928, 1664, 1614, 1429, 1256, 816 cm^{-1}; MS (EI): m/z (%): 206 [M^++H] (16.2), 205 [M^+] (80.2), 68 (100.0); HRMS (EI): m/z: calcd for $C_{13}H_{19}NO$: 205.14666; found: 205.14555.

Double RCM reaction of 2d

Preparation of 6d: Following GP F, a solution of **2d** (40 mg, 0.153 mmol) and **4** (7 mg, 5 mol%) in CH_2Cl_2 (4 mL) was stirred under reflux conditions for 5 h to afford **6d** (26 mg, 83%) as a colorless oil.

RCM reactions of other substrates

Preparation of 6e: Following GP F, a solution of **2e** (90 mg, 0.320 mmol) and **4** (14 mg, 5 mol%) in CH_2Cl_2 (7 mL) was stirred under reflux conditions for 6 h to afford **6e** (64 mg, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.17 (m, 5H), 6.41 (dt, J = 9.2, 4.2 Hz, 1H), 6.10–6.02 (m, 1H), 5.87 (dt, J = 10.0, 1.8 Hz, 1H), 5.07 (d, J = 17.7 Hz, 1H), 3.90–3.68 (m, 2H), 2.77–2.60 (m, 1H), 2.58–2.40 (m, 1H), 2.28–2.06 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2, 138.6, 137.2, 135.1, 128.4, 127.5, 125.1, 124.6, 121.4, 50.8, 43.9, 31.7, 28.9 ppm; IR (neat): $\tilde{\nu}$ = 1669, 1612 cm^{-1}; MS (EI): m/z (%): 226 [M^++H] (16.1), 225 [M^+] (87.3), 130 (100.0); HRMS (EI): calcd for $C_{15}H_{15}NO$: 225.11536; found: 225.11377.

Preparation of 6f: Following GP F, a solution of **2f** (50 mg, 0.181 mmol) and **4** (8 mg, 5 mol%) in CH_2Cl_2 (4 mL) was stirred under reflux conditions for 5 h to afford **6f** (34 mg, 85%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00–6.93 (m, 1H), 6.43 (dt, J = 9.2, 4.1 Hz, 1H), 5.94–5.84 (m, 1H), 5.02 (d, J = 18.5 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.75–3.58 (m, 2H), 2.82–2.66 (m, 1H), 2.60–2.44 (m, 1H), 2.30–2.10 (m, 2H), 1.26 (t, J = 7.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 163.9, 137.0, 136.6, 129.0, 124.5, 60.6, 50.3, 41.7, 31.3, 28.4, 14.2 ppm; IR (neat): $\tilde{\nu}$ = 1710, 1671, 1612, 1251 cm^{-1}; MS (EI): m/z (%): 222 [M^++H] (9.5), 221 [M^+] (54.1), 192 (100.0); HRMS (EI): m/z: calcd for $C_{12}H_{15}NO_3$: 221.10519; found: 221.10223.

Preparation of 6k, 7k, and 8k: Following GP F, a solution of **2k** (130 mg, 0.594 mmol) and **3** (26 mg, 5 mol%) in CH_2Cl_2 (12 mL) was stirred under reflux conditions for 16 h to afford **6k** (14 mg, 15%), **8a** (51 mg, 53%), and **7k** (15 mg, 13%) as liquids. **6k**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.42 (dt, J = 9.5, 4.3 Hz, 1H), 5.91 (dt, J = 9.5, 1.2 Hz, 1H), 5.85–5.62 (m, 2H), 4.46 (d, J = 19.6 Hz, 1H), 3.58 (d, J = 22.0 Hz, 1H), 2.50–2.30 (m, 2H), 2.08–1.90 (m, 2H), 1.30 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 136.8, 124.7, 123.9, 122.4, 54.2, 39.9, 38.3, 38.3, 23.4 ppm; IR (neat): $\tilde{\nu}$ = 2931, 1662, 1605, 1413, 1137, 732 cm^{-1}; MS (EI): m/z (%): 163 [M^+] (71.5), 162 [M^+–H] (92.4), 68 (100.0); HRMS (EI): m/z: calcd for $C_{10}H_{13}NO$: 163.09971; found: 163.09749. **8k**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (dt, J = 5.8, 1.8 Hz, 1H), 6.08 (dt, J = 5.8, 1.8 Hz, 1H),

5.66 (s, 2H), 4.04 (t, J=1.8 Hz, 2H), 2.92 (d, J=14.7 Hz, 2H), 2.49 (d, J=14.7 Hz, 2H), 1.37 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ= 171.5, 141.8, 129.2, 128.3, 62.2, 51.9, 44.8, 24.9 ppm; IR (neat): $\tilde{\nu}$=3398, 2884, 1629, 1408, 1355, 1283, 1217, 1158, 971, 794 cm^{-1}; MS (EI): m/z (%): 163 [M^+] (3.5), 80 (100.0); HRMS (EI): m/z: calcd for $C_{10}H_{13}NO$: 163.09971; found: 163.10095. **7k**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.41 (dd, J=16.5, 9.8 Hz, 1H), 6.29 (dd, J=16.5, 2.4 Hz, 1H), 6.00–5.85 (m, 1H), 5.65–5.50 (m, 3H), 5.34–5.14 (m, 2H), 4.00–3.82 (m, 2H), 2.80 (d, J=15.3 Hz, 2H), 2.55 (d, J=15.3 Hz, 2H), 1.36 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.1, 135.8, 130.8, 128.5, 127.6, 117.1, 66.9, 48.8, 46.1, 25.1 ppm; IR (neat): $\tilde{\nu}$=1657, 1617 cm^{-1}; MS (EI): m/z (%): 191 [M^+] (1.4), 150 [$M^+-C_3H_5$] (19.8), 55 (100.0); HRMS (EI): calcd for $C_{12}H_{17}NO$: 191.13101; found: 191.13110.

Preparation of 6n, 7n, and 8n: Following GP F, a solution of **2n** (105 mg, 0.425 mmol) and **3** (19 mg, 5 mol%) in CH_2Cl_2 (8.5 mL) was stirred under reflux conditions for 14.5 h to afford a mixture of **6n** and **8a** (33 mg, 41%) and **7n** (33 mg, 35%) as liquids. **6n**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.98–6.80 (m, 1H), 6.10–5.98 (m, 1H), 5.61 (s, 2H), 4.00 (s, 2H), 2.80 (d, J=15.9 Hz, 2H), 2.54 (d, J=15.9 Hz, 2H), 1.30–1.00 (m, 4H), 0.95–0.70 (m, 3H) ppm. **8n**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.40–6.30 (m, 1H), 5.83 (d, J=9.8 Hz, 1H), 5.75–5.50 (m, 2H), 4.49 (d, J= 19.6 Hz, 1H), 3.47 (d, J=19.6 Hz, 1H), 2.38–1.95 (m, 4H), 1.50–1.00 (m, 4H), 0.95–0.70 (m, 3H) ppm; IR (neat): $\tilde{\nu}$=2958, 2931, 1677, 1616, 1439, 1234, 805 cm^{-1}; MS (EI): m/z (%): 176 [M^+-CH_3] (7.6), 162 [$M^+-C_2H_5$] (14.4), 148 [$M^+-C_3H_7$] (100.0). **7n**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.43 (dd, J=16.7, 10.2 Hz, 1H), 6.31 (dd, J=16.4, 2.4 Hz, 1H), 6.02–5.87 (m, 1H), 5.62–5.56 (m, 3H), 5.35–5.15 (m, 2H), 4.00–3.90 (m, 2H), 2.85–2.63 (m, 4H), 1.90–1.80 (m, 2H), 1.30–1.15 (m, 2H), 0.88 (t, J=7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.7, 135.6, 130.5, 128.4, 127.4, 117.0, 70.0, 50.0, 44.0, 40.4, 17.8, 14.5 ppm; IR (neat): $\tilde{\nu}$=1656, 1613 cm^{-1}; MS (ESI): m/z: 220.1 [M^++H]; HRMS (ESI): m/z: calcd for $C_{14}H_{21}NONa$: 242.15209; found: 242.15247.

Preparation of 7l and 8l: Following GP F, a solution of **2l** (80 mg, 0.343 mmol) and **4** (15 mg, 5 mol%) in CH_2Cl_2 (8 mL) was stirred under reflux conditions for 3.5 h to afford **8l** (4 mg, 7%) and **7l** (62 mg, 88%) as liquids. **8l**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.78 (q, J=1.5 Hz, 1H), 5.67 (s, 2H), 3.90 (s, 2H), 2.92 (d, J=15.0 Hz, 2H), 2.50 (br d, J= 16.5 Hz, 2H), 2.02 (d, J=1.5 Hz, 3H), 1.37 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.5, 154.1, 128.6, 124.5, 62.3, 55.0, 45.2, 25.1, 15.1 ppm; IR (neat): $\tilde{\nu}$=2916, 1675, 1390 cm^{-1}; MS (EI): m/z (%): 178 [M^++H] (21.2), 98 (100.0); HRMS (EI): m/z: calcd for $C_{11}H_{15}NO$: 177.11536; found: 177.11635. **7l**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.35–6.25 (m, 2H), 5.60 (br s, 2H), 5.56 (dd, J=8.4, 4.1 Hz, 1H), 5.00 (s, 1H), 4.91 (s, 1H), 3.71 (s, 2H), 2.81 (d, J=14.9 Hz, 2H), 2.56 (d, J=14.9 Hz, 2H), 1.73 (s, 3H), 1.38 (s, 3H) 6ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ= 167.8, 142.4, 130.5, 128.2, 127.4, 112.3, 66.6, 51.9, 45.6, 24.8, 20.1 ppm; IR (neat): $\tilde{\nu}$=1660, 1611, 1415, 1208 cm^{-1}; MS (ESI): m/z: 206.1 [M^++H]; HRMS (ESI): m/z: calcd for $C_{13}H_{19}NONa$: 228.13644; found: 228.13548.

RCM reaction of 14aA with 4 as the catalyst: Following GP F, a solution of **14aA** (179 mg, 1.0 mmol) and **4** (9 mg, 1 mol%) in CH_2Cl_2 (20 mL) was stirred under reflux conditions for 3 h to afford **16l** (129 mg, 85%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.16 (dd, J=17.1, 1.8 Hz, 1H), 5.95 (dd, J=17.1, 9.8 Hz, 1H), 5.75–5.40 (m, 4H), 2.67 (d, J=15.1 Hz, 2H), 2.36 (d, J=15.0 Hz, 2H), 1.40 (s, 3H) ppm; IR (neat): $\tilde{\nu}$=1674, 1657, 1556, 1625 cm^{-1}; MS (EI): m/z (%): 151 [M^+] (1.0), 80 (100.0); elemental analysis calcd for $C_9H_{13}NO$: C 71.49, H 8.67, N 9.26; found: C 71.25, H 8.44, N 9.05.

Preparation of 7m and 8m: Following GP F, a solution of **2m** (87 mg, 0.316 mmol) and **4** (13 mg, 5 mol%) in CH_2Cl_2 (8 mL) was stirred under reflux conditions for 11 h to afford **8m** (5 mg, 7%) and **7m** (70 mg, 90%) as liquids. **8m**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.77 (t, J=1.4 Hz, 1H), 5.67 (s, 2H), 3.90 (d, J=1.1 Hz, 2H), 2.92 (d, J=14.7 Hz, 2H), 2.49 (d, J=14.7 Hz, 2H), 2.31 (t, J=8.0 Hz, 2H), 1.60–1.42 (m, 2H), 1.42–1.26 (m, 5H), 0.92 (t, J=7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ= 172.5, 158.9, 128.6, 123.3, 62.3, 53.9, 45.2, 29.8, 29.2, 25.1, 22.4, 13.8 ppm; IR (neat): $\tilde{\nu}$=2929, 1678 cm^{-1}; MS (EI): m/z (%): 220 [M^++H] (1.8), 219 [M^+] (2.6), 140 (100.0); HRMS (EI): m/z: calcd for $C_{14}H_{21}NO$: 219.16232; found: 219.15824. **7m**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.31 (s, 1H), 6.29 (s, 1H), 5.60 (s, 2H), 5.54 (t, J=6.0 Hz, 1H), 5.03 (s, 1H), 4.91 (s, 1H), 3.73 (s, 2H), 2.80 (d, J=14.7 Hz, 2H), 2.54 (d, J=15.3 Hz, 2H), 2.00 (t, J=7.0 Hz, 2H), 1.50–1.20 (m, 7H), 0.90 (t, J=7.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.9, 146.6, 130.6, 128.3, 127.3, 111.3, 66.7, 51.1, 45.6, 33.8, 29.8, 24.8, 22.5, 13.9 ppm; IR (neat): $\tilde{\nu}$=2930, 1660, 1614, 1416 cm^{-1}; MS (ESI): m/z: 248.2 [M^++H]; HRMS (ESI): m/z: calcd for $C_{16}H_{25}NONa$: 270.18339; found: 270.18342.

Preparation of 6h and 8h: Following GP F, a solution of **2h** (135 mg, 0.579 mmol) and **3** (26 mg, 5 mol%) in CH_2Cl_2 (20 mL) was stirred under reflux conditions for 11.5 h to afford **6h** (71 mg, 69.2%) and **8h** (8 mg, 7.8%) as liquids. **6h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.22 (dt, J= 11.6 Hz, 5.5 Hz, 1H), 6.00 (d, J=11.6 Hz, 1H), 5.80–5.69 (m, 1H), 5.68–5.50 (m, 1H), 4.43 (dd, J=16.5, 6.7 Hz, 1H), 3.92–3.75 (m, 2H), 2.50–1.70 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.9, 137.2, 131.0, 128.0, 126.9, 58.8, 39.0, 34.7, 30.3, 29.1, 25.3 ppm; IR (neat): $\tilde{\nu}$=2936, 1642, 1601, 1419, 1286, 1180, 822, 640 cm^{-1}; MS (EI): m/z (%): 177 [M^+] (100.0), 176 [M^+-H] (17.4); HRMS (EI): m/z: calcd for $C_{11}H_{15}NO$: 177.11536; found: 177.11318. **8h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.99 (dt, J=5.8 Hz, 1.2 Hz, 1H), 6.11 (dt, J=5.8 Hz, 2.5 Hz, 1H), 5.90–5.70 (m, 2H), 4.25–4.10 (m, 1H), 3.89 (s, 2H), 2.30–2.00 (m, 4H), 1.90–1.70 (m, 2H), 1.50–1.30 (m, 2H) ppm; IR (neat): $\tilde{\nu}$=2925, 2852, 1673, 1447, 1401, 1243, 801 cm^{-1}; MS (EI): m/z (%): 178 [M^++H] (14.0), 177 [M^+] (42.6), 84 (100.0); HRMS (EI): m/z: calcd for $C_{11}H_{15}NO$: 177.11536; found: 177.11768.

Preparation of 6j: Following GP F, a solution of **2j** (75 mg, 0.304 mmol) and **4** (13 mg, 5 mol%) in CH_2Cl_2 (6 mL) was stirred under reflux conditions for 3.5 h to afford **6j** (45 mg, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.25–6.15 (m, 1H), 5.98 (d, J=11.3 Hz, 1H), 5.35–5.27 (m, 1H), 4.18 (d, J=16.3 Hz, 1H), 3.95 (d, J=16.4 Hz, 1H), 3.85–3.70 (m, 1H), 2.38–2.63 (m, 11H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.6, 136.9, 134.5, 127.7, 123.9, 58.3, 43.7, 33.9, 29.9, 27.7, 25.1, 23.7 ppm; IR (neat): $\tilde{\nu}$=2933, 1644, 1603, 1417 cm^{-1}; MS (EI): m/z (%): 192 [M^++H] (18.0), 191 [M^+] (100.0); HRMS (EI): m/z: calcd for $C_{12}H_{17}NO$: 191.13102; found: 191.13200.

Double RCM reaction of 2g

Preparation of 6A, 6B, 8g, and 5g: Following GP F, a solution of **2g** (105 mg, 0.479 mmol) and **3** (21 mg, 5 mol%) in CH_2Cl_2 (9 mL) was stirred under reflux conditions for 8 h to afford a mixture of **6A** and **6B** (30 mg, **6A**/**6B** 1.3:1, 38%), **8g** (10 mg, 13%) as a liquid, and **5g** (40 mg, 44%). **8g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.04 (dt, J=5.8 Hz, 1.8 Hz, 1H), 6.13 (dt, J=5.8 Hz, 1.8 Hz, 1H), 5.70–5.45 (m, 2H), 4.37–4.18 (m, 1H), 4.00–3.75 (m, 2H), 2.38–1.85 (m, 4H), 1.85–1.50 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.3, 142.8, 128.4, 127.1, 125.1, 49.3, 47.1, 30.0, 27.9, 25.5 ppm; IR (neat): $\tilde{\nu}$=3456, 2919, 1666, 1587 cm^{-1}; MS (EI): m/z (%): 163 [M^+] (13.9), 80 (100.0); HRMS (EI): m/z: calcd for $C_{10}H_{13}NO$: 163.09971; found: 163.09933. **5g** was used for the next step without further characterization.

Preparation of 6A: Following GP F, a solution of **5g** (34 mg, 0.178 mmol) and **4** (5 mg, 3 mol%) in CH_2Cl_2 (5 mL) was stirred under reflux conditions for 2.5 h to afford **6A** (25 mg, 86%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.18 (dt, J=11.7 Hz, 5.9 Hz, 1H), 5.95 (d, J= 11.7 Hz, 1H), 5.90–5.70 (m, 2H), 4.20–4.05 (m, 1H), 3.96–3.75 (m, 2H), 2.45–1.70 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.8, 137.8, 127.8, 125.2, 124.7, 51.8, 42.0, 34.6, 28.9, 25.6 ppm; IR (neat): $\tilde{\nu}$=1652, 1589 cm^{-1}; MS (70 eV, EI): m/z (%): 164 [M^++H] (100.0), 163 [M^+] (4.25); HRMS (EI): m/z: calcd for $C_{10}H_{13}NO$: 163.09971; found: 163.10183.

Characterization of 6A by bromination: Following GP G, a solution of **6A** (25 mg, 0.15 mmol) in CCl_4 (3 mL) was treated with bromine (0.79 mL, 0.389 M in CCl_4, 0.31 mmol) to afford **15g** (30 mg, 40%) as a white solid. M.p. 90–92 °C (recrystallized from dichloromethane/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.19 (d, J=5.4 Hz, 1H), 4.56 (dd, J=9.7, 5.1 Hz, 1H), 4.49–4.35 (m, 2H), 4.30–4.20 (m, 1H), 4.19–4.05 (m, 1H), 3.79 (dd, J=14.0, 7.6 Hz, 1H), 2.66 (ddd, J=14.4, 6.5, 3.5 Hz, 1H), 2.30–2.10 (m, 4H), 2.10–2.00 (m, 1H) ppm; IR (KBr): $\tilde{\nu}$= 1657 cm^{-1}; MS (EI): m/z (%): 488 [M^++H] with 4×^{81}Br (1.9), 486 [M^+ +H] with 3×^{81}Br, 1×^{79}Br (7.8), 484 [M^++H] with 2×^{81}Br, 2×^{79}Br (12.8), 482 [M^++H] with 1×^{81}Br, 3×^{79}Br (9.5), 480 [M^++H] with 4×^{79}Br (3.8), 402 (100.0).

Total synthesis of four stereoisomers of lupinine and its derivatives

General procedure H—Synthesis of (2*S*,3*S*)-21: Anhydrous powdered 4 Å molecular sieves (1.2 g) and anhydrous CH_2Cl_2 (110 mL) were placed in a 250 mL round-bottomed flask under Ar. After cooling the flask to

−20 °C, the following reagents were added sequentially through an addition funnel with stirring: L-(+)-diethyl tartrate (883 mg, 4.29 mmol) in CH_2Cl_2 (1 mL), $Ti(OiPr)_4$ (1.07 mL, 3.56 mmol), and 6.25 M *t*BuOOH in CH_2Cl_2 (11.4 mL, 71.25 mmol). After stirring the reaction mixture for 1 h at −20 °C, a solution of (*E*)-2,5-dihexen-1-ol (3.50 g, 35.71 mmol, previously stored for 24 h over 4 Å molecular sieves) in CH_2Cl_2 (18 mL) was added dropwise. After stirring for 4 h at −20 °C, the reaction was quenched by addition of 10 % aq. NaOH solution (2.86 mL) and diethyl ether (17 mL). The mixture was then allowed to warm to 10 °C before anhydrous $MgSO_4$ (2.86 g) and celite (0.36 g) were added. After stirring at RT for 15 min, the mixure was filtered through a short pad of Celite, the solvents were evaporated, and the excess *t*BuOOH was removed by azeotropic distillation with toluene. The crude product was then purified by column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give (2*S*,3*S*)-**21** (3.484 g, 86 %) as an oil. $[\alpha]_D^{20} = -36.0$ ($c = 1.15$, $CHCl_3$); the enantiomeric excess was determined to be 94.6 % by HPLC analysis of the *p*-toluene sulfonate derviative; HPLC (chiralcel OD column, 0.46 × 25 cm, RT, 254 nm, 0.5 mL min^{-1}, hexane/isopropyl alcohol 9:1): $t_R = 23.94$ min (2*R*,3*R*); $t_R = 25.14$ min (2*S*,3*S*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.90–5.72$ (m, 1H), 5.20–5.05 (m, 2H), 3.91 (ddd, $J = 12.6$, 5.5, 2.2 Hz, 1H), 3.63 (ddd, $J = 12.6$, 7.2, 4.3 Hz, 1H), 3.10–3.00 (m, 1H), 3.00–2.90 (m, 1H), 2.36 (t, $J = 5.3$ Hz, 2H), 1.94 (t, $J = 5.9$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$)δ132.7, 117.7, 61.5, 57.9, 54.7, 35.5 ppm; IR (neat): $\tilde{\nu} = 3435$, 1643, 1082, cm^{-1}; MS (EI): *m*/*z* (%): 43 (100.0).

General procedure I—Synthesis of (3*R*,4*S*)-23: CuI (1.80 g, 9.42 mmol) was suspended in diethyl ether (220 mL) at −20 °C under Ar. Vinyl magnesium bromide (80 mL, 1.2 M solution in THF, 96 mmol) was added through an addition funnel. The solution was stirred for 10 min and then cooled to −78 °C. A solution of epoxide (2*S*,3*S*)-**21** (3.30 g, 28.95 mmol) in diethyl ether (10 mL) was added through an addition funnel. After the addition, the reaction mixture was warmed to −25 °C, stirred for 16 h at this temperature, and quenched with saturated aq. NH_4Cl (80 mL). The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation gave a crude mixture, which was contaminated with the corresponding 1,2-diol. The mixture of the diols was dissolved in THF/water (1:1, 200 mL) and treated with a solution of $NaIO_4$ (6.60 g, 30.84 mmol) in water (40 mL). After stirring for 3 h, solid NaCl (40 g) was added. The aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. Evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate 3:1) gave (3*R*,4*S*)-**23** (2.84 g, 69 %) as a colorless oil. $[\alpha]_D^{20} = -9.2$ ($c = 1.20$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.90–5.73$ (m, 1H), 5.70–5.57 (m, 1H), 5.22–5.08 (m, 4H), 3.88–3.64 (m, 3H), 2.95–2.78 (br s, 1H), 2.70–2.50 (br s, 1H), 2.48–2.27 (m, 2H), 2.20–2.08 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 135.8$, 134.3, 118.8, 118.3, 73.2, 65.3. 51.1. 40.1 ppm; IR (neat): $\tilde{\nu} =$ 3365, 2902, 1641, 1432, 1052, 916 cm^{-1}; MS (ESI): *m*/*z*: 165.1 [M^++Na]; HRMS (ESI): calcd for $C_8H_{14}O_2Na$: 165.08915; found: 165.08856.

General procedure J—Synthesis of (3*R*,4*S*)-24: Et_3N (2.36 mL, 16.96 mmol) and DMAP (265 mg, 2.12 mmol) were added to a solution of (3*R*,4*S*)-**23** (1.58 g, 11.13 mmol) in CH_2Cl_2 (20 mL) at RT, then TBSCl (1.84 g, 12.23 mmol) was added in several portions at −78 °C. After the addition, the reaction mixture was warmed to RT with stirring for 3 h and quenched with saturated aq. NH_4Cl (15 mL) and NaCl (15 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were washed with brine and dried over $MgSO_4$. Evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate 7:1) afforded the corresponding silyl ether as a colorless oil in a quantitative yield, which was used for the next step directly.

Methanesulfonyl chloride (1.23 g, 10.74 mmol) was added to a solution of the silyl ether (2.30 g, 8.98 mmol) and Et_3N (1.75 mL, 12.57 mmol) in dry CH_2Cl_2 (25 mL) at −78 °C. The reaction mixture was warmed to RT and stirred for 1.5 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2, then the combined extracts were washed with brine and dried over $MgSO_4$. Evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate 15:1) gave (3*R*,4*S*)-**24** (2.89 g, 93 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.92–5.65$ (m, 2H), 5.25–5.10 (m, 4H), 4.97–4.90 (m, 1H), 3.78 (dd, $J = 10.5$, 4.8 Hz, 1H), 3.64 (dd, $J =$ 10.5, 4.8 Hz, 1H), 3.01 (s, 3H), 2.70–2.55 (m, 2H), 2.45–2.30 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 134.4$, 132.7, 119.0, 118.9, 82.0, 62.9, 49.4, 38.5, 36.1, 25.8, 18.2, −5.4, −5.6 ppm; IR (neat): $\tilde{\nu} = 2930$, 1642, 1473, 1361, 1177, 1110, 904 cm^{-1}; MS (ESI): *m*/*z*: 357.0 [M^++Na]; elemental analysis calcd for $C_{15}H_{30}SO_4Si$: C 53.85, H 9.04; found: C 54.17, H 9.34.

General procedure K—Synthesis of (3*S*,4*R*)-25: A mixture of (3*R*,4*S*)-**24** (3.30 g, 9.88 mmol) and NaN_3 (2.48 g, 38.15 mmol) in anhydrous HMPA (15 mL) was heated at 40 °C for 2 h with stirring. The reaction mixture was poured into water (30 mL) and extracted with diethyl ether. The combined organic solutions were washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude product was dissolved in dry THF (15 mL) and TBAF (19 mL, 1 M solution in THF, 19 mmol) was added through an addition funnel. The reaction mixture was quenched with saturated aq. NaCl and extracted with diethyl ether, then the combined extracts were dried over $MgSO_4$. Evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate 10:1) gave (3*S*,4*R*)-**25** (1.55 g, 94 %) as a colorless oil. $[\alpha]_D^{20} = -17.5$ ($c =$ 1.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.90–5.60$ (m, 2H), 5.33–5.10 (m, 4H), 3.79–3.56 (m, 3H), 2.50–2.21 (m, 3H), 1.68 (br s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 133.7$, 133.7, 120.2, 118.6, 63.3, 61.6, 50.0, 36.8 ppm; IR (neat): $\tilde{\nu} = 3352$, 2939, 2102, 1643, 1265, 1054 cm^{-1}; MS (EI): *m*/*z* (%): 82 (100.0); elemental analysis calcd for $C_8H_{13}N_3O$: C 57.47, H 7.84, N 25.13; found: C 57.46, H 7.78, N 25.09.

General procedure L—Synthesis of (3*S*,4*R*)-26: (3*S*,4*R*)-**25** (1.50 g, 8.98 mmol) in THF (5 mL) was added slowly to a suspension of NaH (295 mg, 95 % in paraffin oil, 11.68 mmol) in THF (15 mL) through an addition funnel. After the addition, the mixture was stirred for additional 30 min at RT. Then, a solution of BnBr (3.07 g, 11.95 mmol) in THF (5 mL) was added dropwise at RT. After the mixture was stirred at RT for 3.5 h, the reaction mixture was quenched with water and extracted with diethyl ether. The combined organic extracts were washed with brine and dried over $MgSO_4$, then the solvent was evaporated. The crude product was further purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 20:1) to give the corresponding benzyl ether (2.24 g, 97 %) as a colorless oil, which was used for the next step directly without further characterization.

$LiAlH_4$ (14 mL, 1 M solution in THF, 14 mmol) was added to a solution of the benzyl ether (1.80 g, 7.00 mmol) in THF (30 mL) at −78 °C through an addition funnel. After the addition, the reaction mixture was allowed to warm to RT and stirred for 2 h, before Et_2O (30 mL) was added. The reaction was carefully quenched with water (1.5 mL) with cooling (ice/water bath). After filtration through a short pad of celite, the filtrate was dried over $MgSO_4$ and evaporated to give the crude amine (1.58 g, 97 %) as a colorless oil, which was used for the next step directly.

A solution of allyl bromide (0.91 g, 7.52 mmol) in DMF (2 mL) was added slowly to a solution of the amine (1.58 g, 6.82 mmol) and K_2CO_3 (1.88 g, 13.64 mmol) in DMF (12 mL) at 0 °C though a dropping funnel. After the addition, the reaction mixture was stirred for 30 min at the same temperature and then warmed to RT. Water (10 mL) was added after stirring for 1 h. The aqueous layer was extracted with Et_2O, then the combined extracts were washed with brine and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether/ethyl acetate 8:1 with a few drops of Et_3N) gave (3*S*,4*R*)-**26** (1.48 g, 80 %) as a colorless oil. $[\alpha]_D^{20} = -20.3$ ($c = 1.15$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40–7.23$ (m, 5H), 5.92–5.70 (m, 3H), 5.22–5.00 (m, 6H), 4.51 (s, 2H), 3.64 (dd, $J = 9.2$, 6.3 Hz, 1H), 3.52 (dd, $J = 9.2$, 6.3 Hz, 1H), 3.29 (dd, $J = 13.9$, 6.1 Hz, 1H), 3.21 (dd, $J = 13.9$, 6.1 Hz, 1H), 2.82–2.73 (m, 1H), 2.60–2.50 (m, 1H), 2.19 (t, $J = 7.0$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 138.4$, 137.2, 136.8, 136.0, 128.3, 127.5, 127.4, 117.7, 116.9, 115.6, 73.0, 71.2, 57.0, 50.6, 46.6, 36.3 ppm; IR (neat): $\tilde{\nu} = 3074$, 2855, 1640, 1454, 1100, 914, 698 cm^{-1}; MS (ESI): *m*/*z*: 272.1 [M^++H]; HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{25}NONa$: 294.18339; found: 294.18165.

General procedure M—Synthesis of (3*S*,4*R*)-20a: CH_2=CHCOCl (261 mg, 2.88 mmol) was added to a solution of (3*S*,4*R*)-**26** (600 mg, 2.21 mmol) and Et_3N (0.47 mL, 3.32 mmol) in CH_2Cl_2 (13 mL) at −78 °C. After the addition, the reaction mixture was warmed to RT, quenched with water and extracted with diethyl ether. The combined extracts were washed with brine and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) gave (3*S*,4*R*)-**20a** (650 mg, 90 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40–7.20$ (m, 5H), 6.72–6.20 (m, 2H), 6.00–5.75 (m, 4H),

5.20–4.75 (m, 6H), 4.58–3.40 (m, 7H), 2.78–2.22 (m, 3H) ppm; IR (neat): $\tilde{\nu}$ = 3076, 1648, 1612, 1421, 1102, 916 cm^{-1}; MS (EI): *m*/*z* (%): 326 [*M*$^+$+H] (20.4), 91 (100.0); elemental analysis calcd for $C_{20}H_{27}NO_2$: C 77.50, H 8.36, N 4.30; found: C 77.39, H 8.49, N 4.16.

Synthesis of (4*S*,5*R*)-18, (4*S*,5*R*)-19, 28, and 27: Following GP F, (3*S*,4*R*)-**20a** (100 mg, 0.308 mmol) and **3** (14 mg, 5 mol%) in CH_2Cl_2 (5 mL) were stirred under reflux conditions for 52 h to give **27** (60 mg, 66%), (4*S*,5*R*)-**18** (trace), (4*S*,5*R*)-**19** (11 mg, 13%), and **28** (6 mg, 7%) as liquids. **27**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.25 (m, 5H), [6.64 (dd, *J* = 16.8, 10.6 Hz), 6.23 (dd, *J* = 16.8, 10.7 Hz), 1H], [6.26 (dd, *J* = 16.8, 1.9 Hz), 6.45 (dd, *J* = 16.8, 1.9 Hz), 1H], 5.90–5.60 (m, 4H), 5.17–3.37 (series of m, 9H), 2.65–2.55 (m, 1H), 2.45–2.15 (m, 2H) ppm. (4*S*,5*R*)-**18**: $[\alpha]_D^{20}$ = +352.6 (*c* = 0.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.23 (m, 5H), 6.36 (dd, *J* = 9.9, 5.3 Hz, 1H), 5.91 (d, *J* = 9.9 Hz, 1H), 5.81–5.63 (m, 2H), 4.84 (br d, *J* = 18.5 Hz, 1H), 4.51 (s, 2H), 3.81 (br d, *J* = 12.0 Hz, 1H), 3.52–3.32 (m, 3H), 2.58–2.30 (m, 2H), 2.00–1.83 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5, 137.6, 137.6, 128.4, 127.8, 127.6, 125.3, 125.3, 125.2, 73.1, 70.1, 53.2, 42.8, 39.4, 31.0 ppm; IR (neat): $\tilde{\nu}$ = 2853, 1671, 1613, 1455, 1104, 699 cm^{-1}; MS (EI): *m*/*z* (%): 269 [*M*$^+$] (28.9), 91 (100.0); HRMS: calcd for $C_{17}H_{19}NO_2$: 269.14158; found: 269.13981. (4*S*,5*R*)-**19**: $[\alpha]_D^{20}$ = −41.5 (*c* = 0.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.24 (m, 5H), 6.42 (dt, *J* = 9.1, 4.0 Hz, 1H), 5.90 (d, *J* = 9.8 Hz, 1H), 5.87–5.77 (m, 1H), 5.67 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.71 (d, *J* = 18.2 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 3.75–3.60 (m, 1H), 3.51 (d, *J* = 18.3 Hz, 1H), 3.45 (d, *J* = 4.8 Hz, 2H), 2.72–2.57 (m, 2H), 2.43 (dt, *J* = 18.3, 4.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.4, 137.8, 137.4, 128.4, 127.8, 127.6, 125.6, 124.6, 73.2, 71.0, 54.1, 42.1, 39.7, 26.4 ppm; IR (neat): $\tilde{\nu}$ = 2860, 1669, 1614, 1454, 1107, 698 cm^{-1}; MS (EI): *m*/*z* (%): 269 [*M*$^+$] (5.2), 91 (100.00); HRMS: *m*/*z*: calcd for $C_{17}H_{19}NO_2$: 269.14158; found: 269.14095. **28**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.20 (m, 5H), 6.92 (dt, *J* = 6.0, 1.8 Hz, 1H), 6.11 (dt, *J* = 5.7, 2.1 Hz, 1H), 5.90–5.80 (m, 2H), 5.00–4.90 (m, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 3.94 (d, *J* = 20.7 Hz, 1H), 3.82 (d, *J* = 20.7 Hz, 1H), 3.46 (dd, *J* = 9.9, 5.4 Hz, 2H), 3.28 (dd, *J* = 9.3, 6.0 Hz, 1H), 3.22–3.10 (m, 1H), 2.72–2.60 (m, 1H), 2.53–2.41 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 142.6, 138.1, 131.6, 129.4, 128.2, 128.2, 127.5 127.4, 73.2, 68.9, 52.3, 51.6, 48.8, 36.4 ppm; IR (neat): $\tilde{\nu}$ = 2854, 1683, 1452, 1102, 699 cm^{-1}; MS (EI): *m*/*z* (%): 269 [*M*$^+$] (4.0), 91 (100.00); HRMS: *m*/*z*: calcd for $C_{17}H_{19}NO_2$: 269.14158; found: 269.14448.

General procedure N—Synthesis of (+)-1a : Pd/C (16 mg) and two drops of AcOH in MeOH (12 mL) were added to a mixture of (4*S*,5*R*)-**18** and (4*S*,5*R*)-**19** (64 mg, 0.238 mmol) with stirring at 30 °C under H_2 (1 atm) and the mixture was stirred for 24 h. After filtration through a short pad of celite, the reaction mixture was concentrated to give a crude product, which was treated with THF (4 mL) and $LiAlH_4$ (0.5 mL, 1 M solution in THF, 0.5 mmol). The resulting mixture was stirred under reflux conditions for 4 h and treated subsequently with ethyl acetate (2 mL) and saturated aq. NH_4Cl (1 mL). After filtration through a short pad of celite, the filtrate was dried over $MgSO_4$, concentrated, and purified by flash column chromatography on silica gel (ethyl acetate/methanol 3:1 with a few drops of Et_3N) to give (+)-**1a** (38 mg, 95%) as a white solid. M.p. 78–79 °C (recrystallized from diethyl ether/hexane, lit.: 78–79 °C[4h]); $[\alpha]_D^{20}$ = +32.6 (*c* = 0.72, EtOH) (lit.: +31.2 (c = 0.86, EtOH)[4h]); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (dd, *J* = 10.9, 3.5 Hz, 1H), 3.54 (dd, *J* = 10.9, 5.9 Hz, 1H), 2.80 (t, *J* = 12.3 Hz, 2H), 2.30–1.52 (m, 12H), 1.48–1.34 (m, 1H), 1.32–1.10 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.5, 64.3, 56.8, 56.5, 43.8, 29.6, 28.1, 25.5, 24.9, 24.5 ppm; IR (neat): $\tilde{\nu}$ = 3172, 2927, 1471, 1442, 1067 cm^{-1}; MS (EI): *m*/*z* (%): 169 [*M*$^+$] (51.7), 83 (100.0); HRMS: *m*/*z*: calcd for $C_{10}H_{19}NO$: 169.14667; found: 169.14905.

Synthesis of (−)-1a: Following GP N, the reaction of (4*R*,5*S*)-**18**, (4*R*,5*S*)-**19** (80 mg, 0.297 mmol), Pd/C (20 mg), two drops of AcOH, MeOH (12 mL), and $LiAlH_4$ (0.6 mL, 1 M, solution in THF, 0.6 mmol) in THF (6 mL) yielded (−)-**1a** (47 mg, 94%) as a white solid. M.p. 78–79 °C (diethyl ether/hexane, lit.: 78–79 °C[4h]); $[\alpha]_D^{20}$ = −33.0 (*c* = 0.72, EtOH) (lit.: −30.5 (*c* = 8.4, EtOH)[4h]); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (dd, *J* = 10.8, 3.4 Hz, 1H), 3.53 (dd, *J* = 10.6, 5.8 Hz, 1H), 2.79 (t, *J* = 12.2 Hz, 2H), 2.50–2.10 (br s, 1H), 2.10–1.10 (m, 14H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.4, 64.3, 56.8, 56.6, 43.8, 29.6, 28.2, 25.5, 24.9, 24.5 ppm; IR (neat): $\tilde{\nu}$ = 3171, 2927, 1471, 1067, 1015 cm^{-1}; MS (EI): *m*/*z* (%): 169 [*M*$^+$] (86.2), 152 (100.0); HRMS: *m*/*z*: calcd for $C_{10}H_{19}NO$: 169.14667; found: 169.14473.

Synthesis of (−)-1b: Following GP N, the reaction of (4*R*,5*R*)-**18**, (4*R*,5*R*)-**19** (55 mg, 0.204 mmol), Pd/C (13 mg), two drops of AcOH, MeOH (12 mL), and $LiAlH_4$ (0.4 mL, 1 M solution in THF, 0.4 mmol) in THF (4 mL) yielded (−)-**1b** (32 mg, 93%) as a white solid. M.p. 70–71 °C (diethyl ether/hexane, lit.: 70–71 °C[4g]); $[\alpha]_D^{20}$ = −21 (*c* = 0.25, EtOH) [lit.: −21 (*c* = 9.5, EtOH)[4g]); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.70–5.30 (br s, 1H), 4.22–4.12 (m, 1H), 3.70 (d, *J* = 10.8 Hz, 1H), 2.88–2.77 (m, 2H), 2.23–1.45 (m, 13H), 1.28–1.18 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 66.1, 65.1, 57.1, 57.0, 38.0, 31.6, 29.7, 25.6, 24.6, 23.0 ppm; IR (neat): $\tilde{\nu}$ = 3173, 2920, 1471, 1448, 1300, 1067, 1014 cm^{-1}; MS (EI): *m*/*z* (%): 169 [*M*$^+$] (75.4), 152 (100.0); HRMS: calcd for $C_{10}H_{19}NO$: 169.14667; found: 169.14171.

Synthesis of (+)-1b: Following GP N, the reaction of (4*S*,5*S*)-**18**, (4*S*,5*S*)-**19** (55 mg, 0.204 mmol), Pd/C (13 mg), two drops of AcOH, MeOH (12 mL), and $LiAlH_4$ (0.4 mL, 1 M solution in THF, 0.4 mmol) in THF (4 mL) yielded (+)-**1b** (32 mg, 93%) as a white solid. M.p. 68–69 °C (diethyl ether/hexane, lit.: 67–68 °C[4f]); $[\alpha]_D^{20}$ = +20.8 (*c* = 0.40, EtOH) (lit.: +19.5 (*c* = 1, EtOH)[4f]); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.73–5.30 (br s, 1H), 4.23–4.14 (m, 1H), 3.70 (d, *J* = 10.8 Hz, 1H), 2.90–2.75 (m, 2H), 2.25–1.45 (m, 13H), 1.35–1.18 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 66.1, 65.1, 57.1, 57.0, 38.0, 31.5, 29.7, 25.6, 24.6, 23.0 ppm; IR (neat): $\tilde{\nu}$ = 3173, 2920, 1471, 1448, 1067, 1014 cm^{-1}; MS (EI): *m*/*z* (%): 169 [*M*$^+$] (72.1), 152 (100.0); HRMS: *m*/*z*: calcd for $C_{10}H_{19}NO$: 169.14667; found: 169.14446.

Synthesis of 29: $[K_3Fe(CN)_6]$ (147 mg, 0.447 mmol), K_2CO_3 (62 mg, 0.447 mmol), $NaHCO_3$ (37 mg, 0.447 mmol), $CH_3SO_3NH_2$ (14 mg, 0.149 mmol), DHQ-PHAL (2.5 mg, 3.21×10^{-3} mmol), and $K_2OsO_2(OH)_4$ (1 mg, 2.70×10^{-3} mmol) were dissolved in *t*BuOH/H_2O (1:1, 2.4 mL). The mixture was stirred at RT until both phases were clear and then cooled to 0 °C. A solution of (4*R*,5*S*)-**18** (40 mg, 0.149 mmol) in *t*BuOH (1.2 mL) was added all at once and then the heterogeneous slurry was stirred vigorously at 0 °C for 4 h. The reaction was quenched with saturated aq. sodium sulfite (2 mL) and stirred for a further 10 min. The reaction mixture was extracted several times with ethyl acetate and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by flash column chromatography on silica gel (ethyl acetate) gave **29** (37 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ = −255.4 (*c* = 0.900, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.22 (m, 5H), 6.42 (dd, *J* = 10.1, 5.1 Hz, 1H), 5.86 (dd, *J* = 10.1, 0.8 Hz, 1H), 4.51 (s, 2H), 4.44 (td, *J* = 12.5, 5.0 Hz, 2H), 4.10 (br s, 1H), 3.98–3.87 (m, 1H), 3.73–3.60 (m, 1H), 3.45 (d, *J* = 6.9 Hz, 2H), 3.30–3.17 (m, 1H), 2.86 (t, *J* = 11.6 Hz, 1H), 2.52–2.40 (m, 1H), 1.90–1.75 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5, 139.6, 137.6, 128.5, 127.8, 127.7, 124.1, 73.2, 70.8, 67.9, 67.4, 50.6, 44.0, 39.1, 37.1 ppm; IR (neat): $\tilde{\nu}$ = 3387, 1665, 1601, 1079 cm^{-1}; MS (ESI): *m*/*z*: 304.2 [*M*$^+$+H]; HRMS (ESI): *m*/*z*: calcd for $C_{17}H_{22}NO_4$: 304.15488; found: 304.15543.

Synthesis of 30: A mixture of lactam **29** (33 mg, 0.109 mmol), 10% Pd/C (15 mg), AcOH (two drops), and MeOH (6 mL) was stirred at room temperature under H_2 (1 atm) for 24 h. Filtration through Celite and concentration gave the crude product **29A**, which was used for the next step without characterization.

Lactam **29A** in dry THF (5 mL) was treated with a solution of $Me_2S{\cdot}BH_3$ (5 M in THF, 0.2 mL, 1 mmol) under Ar. After 2 h at RT and 1 h under reflux conditions, the excess reducing reagent was decomposed by careful addition of EtOH (1 mL) at −5 °C. After evaporation, the residue was purified by flash column chromatography on silica gel (methanol/ethyl acetate 10:1) to give **30** (20 mg, two steps: 91%) as a white solid. M.p. 180–182 °C (recrystallized from $CHCl_3/CH_3OH$); $[\alpha]_D^{20}$ = 63.0 (*c* = 0.300, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 3.90–3.82 (m, 1H), 3.59 (ddd, *J* = 11.1, 4.6, 2.7 Hz, 1H), 3.47 (dd, *J* = 11.1, 3.7 Hz, 1H), 3.35 (dd, *J* = 11.1, 5.2 Hz, 1H), 2.70 (br d, *J* = 11.2 Hz, 1H), 2.51 (dd, *J* = 10.7, 4.7 Hz, 1H), 2.31 (t, *J* = 11.2 Hz, 1H), 2.12–1.95 (m, 3H), 1.80–1.68 (m, 1H), 1.68–1.45 (m, 2H), 1.33–1.05 (m, 3H) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ = 69.3, 68.4, 64.7, 58.5, 57.3, 57.0, 44.7, 36.1, 39.3, 25.8 ppm; IR (neat): $\tilde{\nu}$ = 3324, 2925, 1462, 1289, 1083, 1070 cm^{-1}; MS (ESI): *m*/*z*: 202.1 [*M*$^+$+H]; HRMS (ESI): *m*/*z*: calcd for $C_{10}H_{19}NO_3Na$: 224.12627; found: 224.12505.

Synthesis of 31: $TsOH\cdot H_2O$ (8 mg) was added to a stirred solution of diol **29** (49 mg, 0.162 mmol) in 2,2-dimethoxypropane (2.5 mL) was added after stirring at 0 °C for 2 h. The reaction was then diluted with CH_3CO_2Et, neutralized with a saturated aq. $NaHCO_3$ solution, and extracted with diethyl ether. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was then purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 1:3) to give **31** (51 mg, 92%) as a colorless oil. $[\alpha]_D^{20} = -111.3$ ($c = 0.600$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$–7.24 (m, 5H), 6.23 (dd, $J = 9.9$, 3.8 Hz, 1H), 5.94 (dd, $J = 9.9$, 2.1 Hz, 1H), 4.52 (s, 2H), 4.41–4.30 (m, 2H), 3.83 (ddd, $J = 10.5$, 7.7, 2.7 Hz, 1H), 3.69 (ddd, $J = 18.4$, 14.1, 8.7 Hz, 2H), 3.49 (ddd, $J = 15.6$, 9.1, 6.1 Hz, 2H), 2.54–2.43 (m, 1H), 2.01 (dt, $J = 14.2$, 1.9 Hz, 1H), 1.81 (ddd, $J = 14.8$, 11.9, 3.1 Hz, 1H), 1.49 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.2$, 139.9, 137.6, 128.4, 127.8, 127.5, 124.9, 108.4, 73.2, 71.1, 70.8, 69.9, 49.8, 41.6, 39.9, 32.2, 27.3, 25.0 ppm; IR (neat): $\tilde{\nu} = 2989$, 1655, 1606, 1436, 1053 cm^{-1}; MS (ESI): m/z: 344.2 [M^++H]; HRMS (ESI): calcd for $C_{20}H_{26}NO_4$: 344.18618; found: 344.18652.

Synthesis of 32: NMO (28 mg, 0.210 mmol) and an aqueous solution of OsO_4 (43 μL, 0.0492 M in H_2O) were added to **31** (36 mg, 0.105 mmol) in CH_3CN (1.5 mL) with stirring. The reaction mixture was stirred at RT for 24 h, concentrated and purified by flash column chromatography on silica gel (ethyl acetate) to give **32** (33 mg, 83%) as a colorless oil. $[\alpha]_D^{20} = -58.5$ ($c = 1.000$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$–7.24 (m, 5H), 4.55 (d, $J = 1.1$ Hz, 2H), 4.40 (dd, $J = 13.6$, 6.4 Hz, 1H), 4.36–4.26 (m, 2H), 4.20–4.10 (m, 1H), 4.10–4.00 (br s, 1H), 3.96 (d, $J = 2.2$ Hz, 1H), 3.74 (dd, $J = 9.2$, 7.6 Hz, 1H), 3.59 (dd, $J = 9.2$, 4.9 Hz, 1H), 3.55–3.41 (m, 1H), 3.00–2.88 (br s, 1H), 2.85 (dd, $J = 13.7$, 8.6 Hz, 1H), 2.42 (dt, $J = 14.8$, 2.4 Hz, 1H), 1.96–1.82 (m, 1H), 1.63 (ddd, $J = 15.6$, 12.10, 4.0 Hz, 1H), 1.49 (s, 3H), 1.35 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.0$, 137.7, 128.5, 127.8, 127.6, 109.0, 73.4, 71.3, 70.5, 70.3, 68.8, 66.8, 50.4, 43.2, 42.3, 34.3, 28.1, 25.9 ppm; IR (neat): $\tilde{\nu} = 3438$, 2925, 1651, 1062 cm^{-1}; MS (ESI): m/z: 378.2 [M^++H]; HRMS (ESI): calcd for $C_{20}H_{28}NO_6$: 378.19166; found: 378.19273.

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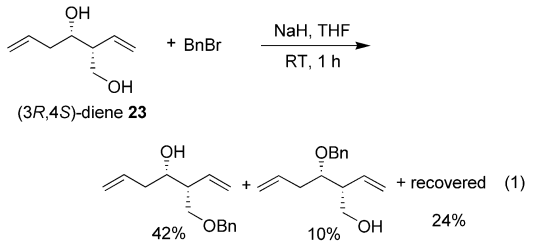
[26] a) J. A. Rao, M. P. Cava, *J. Org. Chem.* **1989**, *54*, 2751; (*Z*)-2,5-dihex-en-1-ol (*cis*/*trans* = 99:1, determined by GC analysis) was prepared by the reduction of hex-2-yn-5-en-1-ol with the Zn–Cu couple in methanol (sealed tube, 120 °C) in 80 % yield.

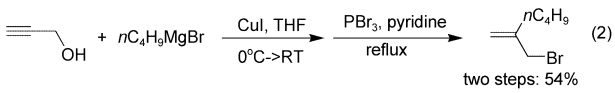
[27] Direct monobenzylation of (3*R*,4*S*) diene **23** yielded two benzyl ethers with a low selectivity [Eq. (1)].



[28] Prepared lupinine was treated with excess Et_3N and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.0 equiv) to furnish the corresponding diastereomeric esters. The *ee* value of the lupinine could then be determined by integration of the CF_3 singlets in the ^{19}F NMR spectrum of these Mosher's esters.

[29] Crystal data for **36**: $C_{10}H_{19}NO_3$, $M_w = 201.26$, orthorhombic, space group $P2(1)2(1)2(1)$, $Mo_{K\alpha}$ radiation; final R indices ($I > 2\sigma(I)$) $R1 = 0.0410$, $wR2 = 0.0732$; $a = 7.5359(8)$, $b = 10.2396(10)$, $c = 13.7251(14)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 1059.09$ (19) Å^3, $T = 293$ (2) K, $Z = 4$; reflections collected/unique 6464/2468 ($R_{int} = 0.0516$), not observed ($I > 2\sigma(I)$) 1941, parameters 204. CCDC-218925 contains the supplementary crystallographic data for **36**. These data can be obtained as described in ref. [22].

[30] Compound **12d** was prepared according to Equation (2).



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