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Stereoselective synthesis of (−)-centrolobine

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ABSTRACT

The stereoselective synthesis of (−)-centrolobine has been accomplished starting from D-glyceraldehyde acetonide by a combination of chelation-controlled diastereoselective alkylation and ring-closing metathesis. A high degree of 1,3-asymmetric induction has been realized in an ether system.

1. Introduction

A large number of cyclic ethers have been isolated from a wide range of organisms with a broad range of biological activity.[1] Some compounds of this class contain a six-membered tetrahydropyran ring usually with a *syn*-stereochemistry in the alkyl substituents on both carbons flanking the ether linkage.[2] For example, (−)-centrolobine (Fig. 1) has been the subject of significant synthetic effort due to its tetrahydropyran ring structure and unique biological activities. (−)-Centrolobine, isolated from the heartwood of *Centrolobium robustum* and the stem of *Brosimum potabile*,[3] exhibits anti-inflammatory, and antibacterial as well as anti-leishmanial activity.[4] A handful of stereoselective syntheses of centrolobine have been reported in the literature.[5]

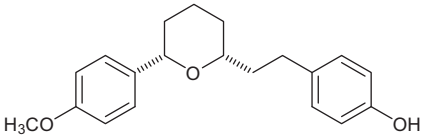

Figure 1. Structure of (−)-centrolobine.

However, based on the conformational preference of *cis*-over *trans*-2,6-disubstituted tetrahydropyran, many of the previous methods have relied on various cycloetherification reactions using pre-installed chiral alcohol. However, the synthesis of centrolobine using a cycloetherification method has the limitation of being only applicable to six-membered cyclic ethers. Thus, the stereoselective synthesis of cyclic ether derivatives with different ring sizes, including six-membered tetrahydropyrans, requires a more general method for the construction of the ring units. Considering the availability of ring-closing metathesis (RCM) developed by Grubbs et al.[6] the stereoselective creation of two stereogenic centers around an ether oxygen has become a key approach for the general synthesis of numerous cyclic ethers with different sizes, having alkyl substituents on both the carbons flanking the ether linkage. Our interest in this molecule is due to our recent success with chelation-controlled stereoselective alkylation.[7] Herein we report on an extension of this methodology to the asymmetric synthesis of (−)-centrolobine.

Our synthetic strategy for (−)-centrolobine is outlined in Scheme 1, which involved a chelation-controlled stereoselective alkylation and RCM reaction as the key steps. It was anticipated that the diastereoselective alkylation of chiral benzyloxyacetic acid **3** derived from chiral auxiliary **4**, followed by the functional group transformation of **2** would furnish acyclic diene **1** with the requisite stereogenic center around the ether oxygen. Cyclization of acyclic diene **1** via RCM using Grubbs catalyst, followed by functional group elaboration would provide the target compound (−)-centrolobine.

2. Results and discussion

The synthesis of (−)-centrolobine started with the preparation of chiral acetamide **5** as a substrate for the stereoselective alkylation reaction (Scheme 2). Chiral benzyl alcohol **4**, readily prepared from D-glyceraldehyde acetonide,[8] was conjugated by a benzyl ether linkage. Treatment of **4** with NaH, followed by O-alkylation with 2-chloro-*N*,*N*-diethylacetamide in dimethoxyethane at −10 °C afforded the chiral auxiliary-conjugated acetamide **5** in 80% yield. Generation of the corresponding enolate of **5** was carried out with LHMDS in THF at −78 °C. The subsequent addition of 1-(benzyloxy)-4-(2-iodoethyl)benzene produced an 11:1 ratio of the *syn*-isomer **6a** and *anti*-isomer **6b**, isolated in 57% and 5% yields, respectively. The absolute configuration of the newly created stereogenic center on **6a** could not be established at the present stage, but it was tentatively assigned as (*S*) on the basis of our proposed chelation model as shown in Figure 2.[7a] The preferential formation of **6a** over **6b** could be rationalized by considering the following chelation model of a highly organized enolate complex,

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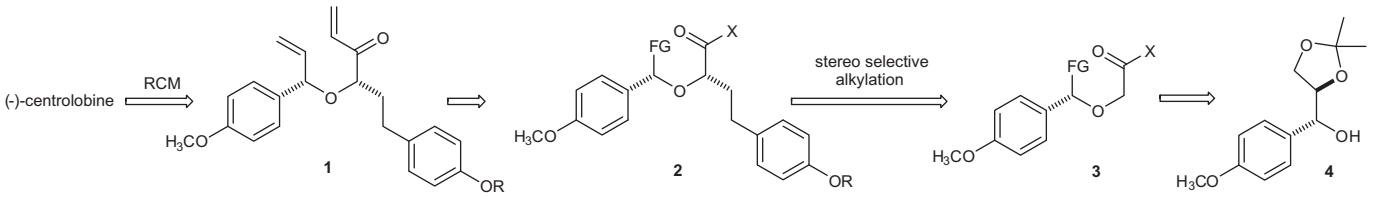
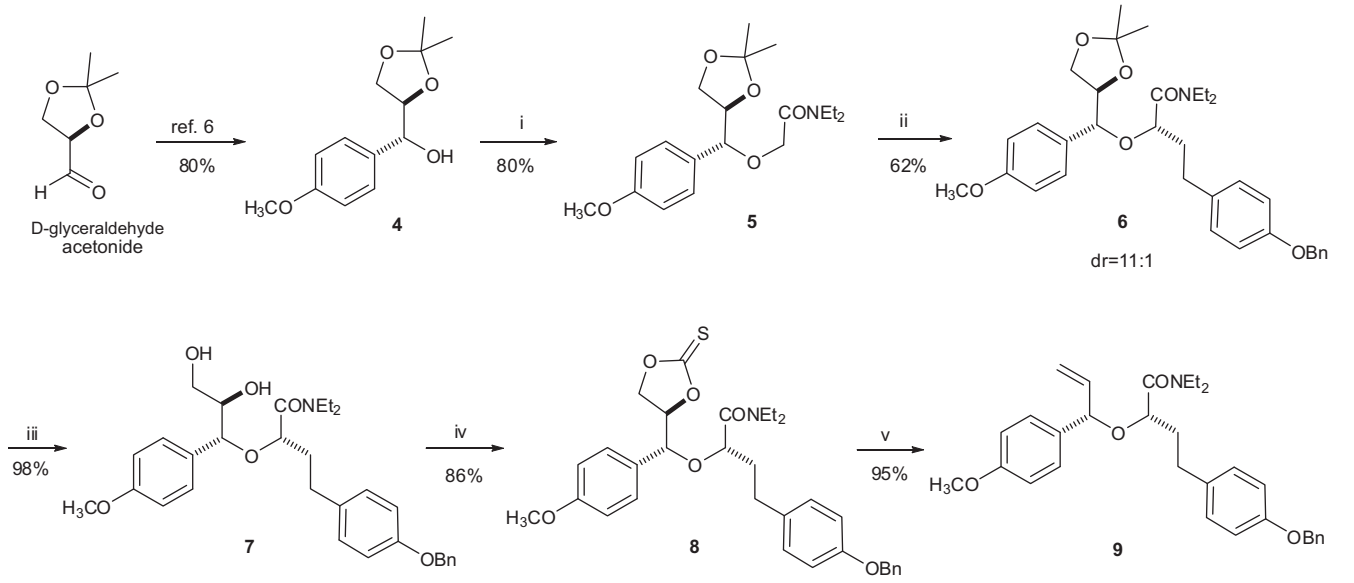


Scheme 1. Retrosynthetic analysis for (−)-centrolobine.



Scheme 2. Synthesis of dialkylated ether **9**. Reagents and conditions: (i) NaH, DME, −10 °C, then $ClCH_2CONEt_2$; (ii) LHMDS, THF, −78 to 10 °C, then 4-benzyloxyphenethyl iodide; (iii) PPTS, MeOH, reflux; (iv) TCDI, toluene, reflux; (v) $P(OMe)_3$, reflux.

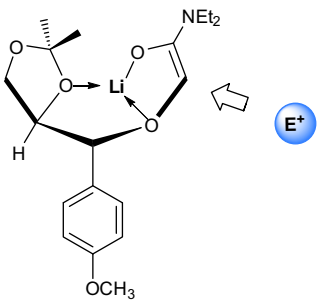


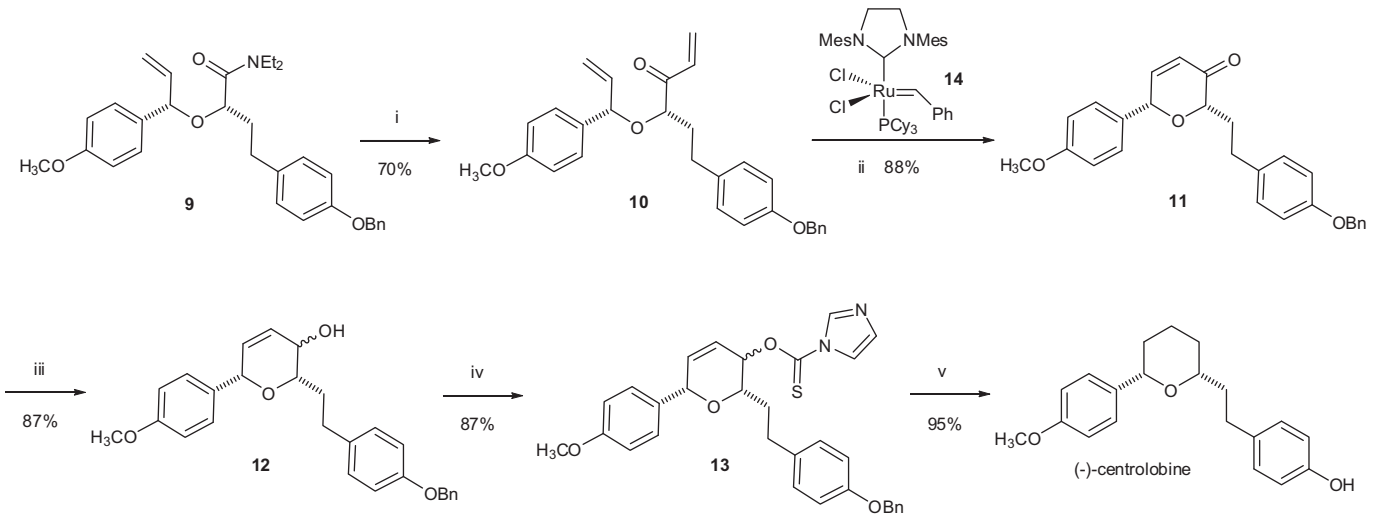
Figure 2. Plausible transition state for alkylation.

which resulted from tridentate chelation of the internal two oxygens with a lithium ion.

In this model, the cyclic ring containing an enolate is puckered to thus minimize the steric interaction with the nearby aromatic ring. Thus, the electrophile approaches from the less hindered convex side. Deprotection of the acetonide group on **6a** was effected with pyridinium *p*-toluenesulfonate in refluxing methanol, to give diol **7** in 98% yield. The reaction of diol **7** with thiocarbonyldiimidazole (TCDI) in refluxing toluene gave the cyclic thiocarbonate **8** in 86% yield. Upon exposure to trimethyl phosphite at reflux, cyclic thiocarbonate **8** underwent reductive elimination to form the desired vinyl compound **9** in 95% yield.

After installing the vinyl group, we next turned out attention to the preparation of the requisite second vinyl group for the RCM reaction. The subsequent cyclization and completion of the synthesis of (−)-centrolobine is shown in Scheme 3.

An alkoxy group at its α-position enables amide **9** to form stable chelates upon treatment with organometallics, and does not regenerate an electrophilic carbonyl group in situ for further reaction, that is, amide **9** could act in the same way as a Weinreb amide toward a Grignard reagent.[9] Thus, when **9** was treated with vinylmagnesium bromide at room temperature, the desired dienyl ketone **10** was obtained in 70% yield. The stage was set for the RCM. Exposure of diene **10** to the 2nd generation Grubbs' catalyst[10] **14** in dichloromethane at room temperature gave cyclohexenone **11** in 88% yield. Treatment of enone **11** with $LiAlH_4$ in refluxing THF produced alcohol **12** as a 2:1 inseparable mixture of epimers in 87% isolated yield. The hydroxyl group could be transformed into the corresponding thiocarbamate by treating **12** with TCDI in refluxing toluene. After conversion to the thiocarbamate, the two epimers became separable by silica gel chromatography, and were isolated in 63% and 24% yields. However, the separation of the two epimers was not important since the newly created stereogenic centers were destined to be removed. The major and minor epimers were combined for the next step. The conversion routes to centrolobine with a variety of reagents and conditions were explored and a one pot reaction from **13** to centrolobine was discovered. By treatment with Raney–Nickel in ethanol under a hydrogen atmosphere, **13** underwent deoxygenation, debenzylation, and double bond reductions concomitantly to generate (−)-centrolobine in 95% yield. The synthetic centrolobine was identical in all aspects (^1H NMR, ^{13}C NMR and IR) to those reported for natural (−)-centrolobine. The specific rotation of the synthetic sample $\{[\alpha]_D^{27} = -89.3$ (*c* 1, $CHCl_3$)} was virtually identical to the value reported by Alcantara et al. $\{[\alpha]_D = -92.2$ (*c* 1, $CHCl_3$)}.[3d]



Scheme 3. Synthesis of (−)-centrolobine starting from dialkylated ether **9**. Reagents and conditions: (i) vinylmagnesium bromide, THF, rt; (ii) **14**, CH_2Cl_2, rt; (iii) $LiAlH_4$, THF, reflux; (iv) TCDI, toluene, reflux; (v) H_2, Ra-Ni, EtOH, rt.

3. Conclusion

In conclusion, we have shown that (−)-centrolobine can be prepared efficiently from D-glyceraldehyde acetonide with 14% overall yield in 11 steps involving chelation-controlled diastereoselective alkylation and ring-closing metathesis. The stereoselective creation of two stereogenic centers around the ether oxygen has been successfully achieved based on 1,3-asymmetric induction, which has rarely been realized before in an ether system. Thus, the combination of a chelation-controlled asymmetric induction and an RCM might hold great potential as a solution for the general synthesis of a variety of cyclic ethers with different sizes, having alkyl substituents on both carbons flanking the ether linkage.

4. Experimental

4.1. General

Optical rotations were measured on a JASCO DIP 1000 digital polarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Inova 400 spectrometer and the chemical shifts are reported as values in parts per million (δ) relative to tetramethylsilane (TMS) as the internal standard. The infrared spectra (IR) were recorded on a JASCO FT/IR-430 spectrophotometer. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck precoated silica gel glass plates ($60F_{254}$). Column chromatography was performed using the forced flow of the indicated solvent on Merck Kieselgel 60 (230–400 mesh). Unless otherwise noted, the materials were obtained from commercially available sources and were used without further purification. THF was freshly distilled from sodium benzophenone ketyl under an argon atmosphere. DCM, DME, and toluene were freshly distilled under a nitrogen atmosphere with calcium hydride.

4.2. 2-((*R*)-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)(4-methoxyphenyl)methoxy)-*N*,*N*-diethylacetamide 5

To a solution of alcohol **4** (1.7 g, 7.1 mmol) in anhydrous dimethoxyethane (7 mL) was added NaH (60% in oil, 700 mg, 17.5 mmol) portionwise at room temperature. After 0.5 h, a solution of 2-chloro-*N*,*N*-diethylacetamide (1.3 mL, 9.2 mmol) in DME (2 mL) was added to the reaction mixture at −10 °C. The mixture was then stirred at this temperature for 2 h, quenched with methanol and H_2O (2 mL), then concentrated in vacuo. The resulting crude residue was diluted with EtOAc (20 mL). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 33% ethyl acetate in hexane to give the alkoxy amide **5** as an oil (2.0 g, 80%): $[\alpha]_D^{28} = -67.5$ (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.42 (m, 2H), 4.12 (d, *J* = 13.6 Hz, 1H), 3.98 (d, *J* = 13.6 Hz, 1H), 3.80 (s, 3H), 3.66 (dd, *J* = 6.0, 8.4 Hz, 1H), 3.57 (dd, *J* = 6.4, 8.4 Hz, 1H), 3.40–3.20 (m, 4H), 1.41 and 1.36 (s, 3H, each), 1.15–1.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 159.8, 129.1, 129.0, 113.9, 109.9, 83.0, 78.9, 67.5, 66.0, 55.2, 41.0, 39.9, 26.6, 25.5, 14.1, 12.8; HRMS (FAB) calcd for $C_{19}H_{30}NO_5$ (M+H) 352.2124, observed 352.2131.

4.3. (*S*)-4-(4-(Benzyloxy)phenyl)-2-((*R*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(4-methoxyphenyl)methoxy)-*N*,*N*-diethylbutanamide 6a

To a solution of amide **5** (351 mg, 1.00 mmol) in anhydrous THF (6 mL) was added dropwise an LHMDS solution (2.00 mL, 2.00 mmol, 1 M in THF) at −78 °C. After 0.5 h, a solution of 1-(benzyloxy)-4-(2-iodoethyl)benzene (1.18 g, 3.50 mmol) in THF (8 mL) was added. The reaction mixture was then stirred at this temperature for 4 h, quenched with brine (20 mL), and extracted with EtOAc (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 30% ethyl acetate in hexane to give 2 diastereomers as a colorless oil. (*S*,*R*,*R*)-**6a** (320 mg, 57%): R_f = 0.50 (*n*-hexane–EtOAc = 1:2); $[\alpha]_D^{28} = -47.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 4.99 (s, 2H), 4.37 (dd, *J* = 6.4, 12.8 Hz, 1H), 4.26 (d, *J* = 6.4 Hz, 1H), 3.97 (dd, *J* = 3.2, 9.2 Hz, 1H), 3.78 (s, 3H), 3.73 (d, *J* = 6.4 Hz, 2H), 3.46 (m, 1H), 3.30–2.90 (m, 3H), 2.79 (m, 1H), 2.46 (m, 1H), 2.09 (m, 1H), 1.77 (m, 1H), 1.36 and 1.34 (s, 3H, each), 1.06 (t, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 159.7, 157.0, 137.1, 133.9, 129.7, 129.4, 128.5, 127.8, 127.4, 114.7, 113.8, 109.8, 80.5, 78.7, 75.0, 70.0, 65.9, 55.2, 40.7, 40.1, 35.0, 31.2, 26.5, 25.7, 14.3, 12.9; IR (NaCl) *v* 2933, 2360, 1649, 1611, 1511, 1455, 1243, 640; HRMS (FAB) calcd for $C_{34}H_{44}NO_6$ (M+H) 562.3169, observed 562.3167. (*R*,*R*,*R*)-**6b** (29 mg, 5%): R_f = 0.45 (*n*-hexane–EtOAc = 1:2); $[\alpha]_D^{28} = -24.4$ (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.28 (m, 5H), 7.18 (d, *J* = 8.4 Hz, 2H),

7.14 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 5.03 (s, 2H), 4.41 (dd, J = 7.6, 14.4 Hz, 1H), 4.24 (d, J = 8.0 Hz, 1H), 4.19 (dd, J = 4.0, 8.8 Hz, 1H), 3.75 (s, 3H), 3.60 (dd, J = 6.4, 8.4 Hz, 1H), 3.40 (dd, J = 7.6, 8.4 Hz, 1H), 3.20–2.70 (m, 6H), 2.09 (m, 1H), 1.80 (m, 1H), 1.38 and 1.35 (s, 3H, each), 0.95–0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 159.7, 157.0, 137.2, 134.1, 130.0, 129.6, 129.0, 128.5, 128.4, 127.8, 127.4, 114.7, 113.7, 110.0, 83.8, 79.3, 76.8, 70.0, 66.0, 55.2, 40.8, 40.1, 35.1, 30.7, 26.7, 25.6, 14.2, 12.7; IR (NaCl) ν 2918, 1648, 1511, 1456, 1378, 1243, 632.

4.4. (*S*)-4-(4-(Benzyloxy)phenyl)-2-((1*R*,2*R*)-2,3-dihydroxy-1-(4-methoxyphenyl)propoxy)-*N*,*N*-diethylbutanamide 7

To a solution of acetonide **6a** (800 mg, 1.42 mmol) in MeOH (20 mL) was added a catalytic amount of PPTS (30 mg). The reaction mixture was then refluxed and stirred for 2 h, cooled down to rt, evaporated to dryness, dissolved in CH_2Cl_2 (50 mL), washed with water (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 40% acetone in hexane to give diol **7** as a colorless oil (726 mg, 98%): R_f = 0.40 (n-hexane–acetone = 3:2); $[\alpha]_D^{25} = -110.4$ (c 0.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.25 (m, 7H), 6.92 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 8.4 Hz, 2H), 5.16 (s, 1H), 4.97 (s, 2H), 4.00 (d, J = 8.0 Hz, 1H), 3.90 (d, J = 8.4 Hz, 1H), 3.80 (m, 4H), 3.65–3.50 (m, 2H), 3.20 (m, 1H), 3.00 (m, 1H), 2.85–2.65 (m, 4H), 2.42 (m, 1H), 2.03 (m, 1H), 1.59 (m, 1H), 1.06 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 159.9, 157.0, 137.0, 133.3, 130.3, 129.5, 129.2, 128.5, 127.9, 127.4, 114.7, 114.1, 82.3, 74.9, 72.7, 69.9, 62.6, 55.3, 40.6, 40.5, 35.6, 30.6, 14.3, 12.9; IR (NaCl) ν 3376, 2932, 1631, 1511, 1454, 1246; HRMS (FAB) calcd for $C_{31}H_{40}NO_6$ (M+H) 522.2856, observed 522.2852.

4.5. (*S*)-4-(4-(Benzyloxy)phenyl)-*N*,*N*-diethyl-2-((*R*)-(4-methoxyphenyl)((*R*)2-thioxo-1,3-dioxolan-4-yl)methoxy)butanamide 8

A mixture of diol **7** (720 mg, 1.38 mmol) and thiocarbonyldiimidazole (295 mg, 1.65 mmol) in toluene (15 mL) was heated at reflux for 1 h, then cooled down to rt, diluted with EtOAc (100 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 20% acetone in hexane to give thiocarbonate **8** as a white foam (670 mg, 86%): R_f = 0.30 (n-hexane–acetone = 3:1); $[\alpha]_D^{25} = -140.8$ (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.25 (m, 7H), 7.00 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.35 (dd, J = 5.2, 8.4 Hz, 1H), 4.99 (s, 2H), 4.94 (m, 1H), 4.61 (t, J = 8.4 Hz, 1H), 4.37 (d, J = 2.0 Hz, 1H), 3.95 (dd, J = 2.0, 8.4 Hz, 1H), 3.79 (s, 3H), 3.49 (m, 1H), 3.06 (m, 1H), 2.90–2.70 (m, 3H), 2.58 (m, 1H), 2.02 (m, 1H), 1.72 (m, 1H), 1.05 (t, J = 7.2 Hz, 3H), 0.71 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 170.2, 160.3, 157.0, 137.1, 133.5, 129.5, 128.5, 127.8, 127.4, 127.0, 114.7, 114.2, 84.0, 77.5, 72.0, 71.1, 69.9, 55.3, 40.9, 40.4, 35.4, 30.5, 14.1, 13.0; IR (NaCl) ν 2929, 2383, 1611, 1511, 1455, 1290; HRMS (FAB) calcd for $C_{32}H_{38}NO_6S$ (M+H) 564.2420, observed 564.2415.

4.6. (*S*)-4-(4-(Benzyloxy)phenyl)-*N*,*N*-diethyl-2-((*S*)-1-(4-methoxyphenyl)allyloxy)butanamide 9

A mixture of thiocarbonate **7** (670 mg, 1.19 mmol) in trimethyl phosphite (10 mL) was heated at reflux for 48 h, then cooled down to rt, evaporated to dryness, dissolved in EtOAc (100 mL), washed with water (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 33% ethyl acetate in hexane to give alkene **8** as a colorless oil (550 mg, 95%): R_f = 0.40 (n-hexane–EtOAc = 1:1); $[\alpha]_D^{25} = -31.2$ (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.20 (m, 7H), 6.92 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 6.02 (m, 1H), 5.15 (m, 2H), 4.99 (s, 2H), 4.72 (d, J = 5.6 Hz, 1H), 3.95 (dd, J = 3.2, 9.2 Hz, 1H), 3.79 (s, 3H), 3.42 (m, 1H), 3.21 (m, 1H), 3.05 (m, 2H), 2.76 (m, 1H), 2.47 (m, 1H), 2.05 (m, 1H), 1.74 (m, 1H), 1.07 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 159.4, 157.0, 139.2, 137.2, 133.8, 132.4, 129.5, 129.0, 128.5, 127.9, 127.4, 115.7, 114.7, 113.9, 80.8, 74.1, 69.9, 55.2, 40.7, 40.2, 35.3, 31.0, 14.3, 12.9; IR (NaCl) ν 2917, 2359, 1653, 1508, 1457, 1243, 636; HRMS (FAB) calcd for $C_{31}H_{38}NO_4$ (M+H) 488.2801, observed 488.2798.

4.7. (*S*)-6-(4-(Benzyloxy)phenyl)-4-((*S*)-1-(4-methoxyphenyl)-allyloxy)hex-1-en-3-one 10

To a solution of amide **9** (470 mg, 0.96 mmol) in THF (10 mL) was added vinyl magnesium bromide (1.44 mL, 1 M in THF, 1.44 mmol) dropwise at room temperature. The reaction mixture was stirred for 1 h, then diluted with EtOAc (100 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 12% EtOAc in hexane to give diene **10** as a colorless oil (300 mg, 70%): R_f = 0.75 (n-hexane–EtOAc = 2:1); $[\alpha]_D^{25} = -38.7$ (c 0.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.20 (m, 7H), 6.94 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 6.77 (m, 1H), 6.36 (d, J = 17.2 Hz, 1H), 5.98 (m, 1H), 5.75 (d, J = 10.4 Hz, 1H), 5.23 (d, J = 17.2 Hz, 1H), 5.15 (d, J = 10.4 Hz, 1H), 5.00 (s, 2H), 4.64 (d, J = 6.4 Hz, 1H), 3.87 (dd, J = 4.0, 8.4 Hz, 1H), 3.79 (s, 3H), 2.68 (m, 1H), 2.46 (m, 1H), 1.93 (m, 1H), 1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 159.4, 157.0, 138.5, 137.1, 133.5, 131.9, 131.4, 130.9, 129.6, 129.3, 128.8, 128.7, 128.5, 127.9, 127.4, 116.2, 114.7, 113.9, 81.9, 80.8, 70.0, 55.3, 34.5, 30.6; IR (NaCl) ν 2918, 2849, 2360, 1698, 1608, 1508, 1241, 636; HRMS (FAB) calcd for $C_{29}H_{30}O_4$ (M^+) 442.2144, observed 442.2143.

4.8. (2*S*,6*S*)-2-(4-(Benzyloxy)phenethyl)-6-(4-methoxyphenyl)-2*H*-pyran-3(6*H*)-one 11

To a solution of diene **10** (300 mg, 0.68 mmol) in CH_2Cl_2 (150 mL, 4.5×10^{-3} M) was added 2nd generation Grubbs' catalyst **14** (29 mg, 0.03 mmol) at room temperature. The reaction mixture was stirred for 8 h, and then evaporated to dryness under reduced pressure, which was purified by column chromatography eluting with 10% EtOAc in hexane to give pyranone **11** as a colorless oil (220 mg, 88%): R_f = 0.30 (n-hexane–EtOAc = 6:1); $[\alpha]_D^{25} = -183.9$ (c 0.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.25 (m, 7H), 7.11 (d, J = 8.8 Hz, 2H), 6.97 (dd, J = 1.6, 10.0 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.15 (dd, J = 2.4, 10.0 Hz, 1H), 5.26 (dd, J = 2.4, 4.0 Hz, 1H), 5.02 (s, 2H), 4.04 (m, 1H), 3.81 (s, 3H), 2.72 (m, 2H), 2.27 (m, 1H), 2.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 159.8, 157.1, 150.9, 137.2, 133.9, 131.4, 129.6, 128.6, 127.9, 127.5, 126.8, 114.8, 114.2, 79.5, 76.5, 70.0, 55.4, 31.4, 30.0; IR (NaCl) ν 2918, 1686, 1611, 1509, 1247, 632; HRMS (FAB) calcd for $C_{27}H_{26}O_4$ (M^+) 414.1831, observed 414.1835.

4.9. (2*S*,6*S*)-2-(4-(Benzyloxy)phenethyl)-6-(4-methoxyphenyl)-3,6-dihydro-2*H*-pyran-3-ol 12

To a suspension of lithium aluminum hydride (15 mg, 0.39 mmol) in THF (2 mL) was added dropwise a solution of pyranone **11** (105 mg, 0.25 mmol) in THF (3 mL) at room temperature.

The reaction mixture was stirred and refluxed for 1 h, then cooled, quenched with 1 drop of water and 20% NaOH, diluted with THF (50 mL), dried over anhydrous K_2CO_3, filtered on Celite, and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 25% EtOAc in hexane to give allylic alcohol **12** as a colorless oil (92 mg, 87%): R_f = 0.20 (*n*-hexane–EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.28 (m, 7H), 7.15 (d, J = 8.8 Hz, 2H), 6.94–6.88 (m, 4H), 6.20–5.80 (m, 2H), 5.10–5.00 (m, 3H), 4.05 (m, 1H), 3.80 (s, 3H), 3.59 (m, 1/3H), 3.35 (m, 2/3H), 2.91–2.65 (m, 2H), 2.17 (m, 1H), 1.85 (m, 1H); HRMS (FAB) calcd for $C_{27}H_{28}O_4$ (M^+) 416.1988, observed 416.1984.

4.10. *O*-(2*S*,6*S*)-2-(4-(Benzyloxy)phenethyl)-6-(4-methoxyphenyl)-3,6-dihydro-2*H*-pyran-3-yl 1*H*-imidazole-1-carbothioate 13

To a solution of allylic alcohol **12** (67 mg, 0.16 mmol) in toluene (3 mL) was added thiocarbonyldiimidazole (86 mg, 0.48 mmol). The reaction mixture was refluxed for 4 h, cooled to rt, and evaporated to dryness. The crude product was purified by column chromatography eluting with 25% EtOAc in hexane to give two diastereomers as a colorless oil. Major (54 mg, 63%): R_f = 0.20 (*n*-hexane–EtOAc = 2:1); $[\alpha]_D^{25} = +44.5$ (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.45–7.28 (m, 8H), 7.10–6.80 (m, 7H), 5.91 (m, 2H), 5.02 (s, 2H), 4.55–4.30 (m, 3H), 3.77 (s, 3H), 2.70 (m, 2H), 1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 159.8, 157.0, 137.1, 135.4, 134.1, 133.1, 130.9, 130.8, 129.4, 128.6, 128.5, 127.9, 127.4, 126.2, 115.9, 114.7, 113.8, 78.8, 74.5, 70.0, 55.2, 46.9, 36.8, 29.9; IR (NaCl) ν 3032, 2925, 2837, 1696, 1612, 1512, 1249, 629; HRMS (FAB) calcd for $C_{31}H_{31}N_2O_4S$ (M+H) 527.2005, observed 527.2003. Minor (21 mg, 24%): R_f = 0.22 (*n*-hexane–EtOAc = 2:1); $[\alpha]_D^{25} = -195.1$ (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.45–7.24 (m, 8H), 7.15–6.80 (m, 7H), 6.15 (m, 1H), 5.88 (d, J = 10.0 Hz, 1H), 5.07 (s, 1H), 5.02 (s, 2H), 4.60–4.30 (m, 2H), 3.73 (s, 3H), 2.78 (m, 2H), 1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 159.0, 157.1, 137.1, 135.4, 134.0, 133.5, 130.9, 130.6, 129.4, 128.5, 127.9, 127.4, 127.0, 124.9, 115.9, 114.8, 113.4, 76.3, 75.1, 70.0, 55.2, 47.0, 36.8, 30.2; IR (NaCl) ν 3032, 2929, 2836, 1689, 1613, 1512, 1467, 1247, 884.

4.11. 4-(2-((2*R*,6*S*)-6-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-2-yl)ethyl)phenol (centrolobine)

To a solution of thiocarbamate **10** (50 mg, 0.095 mmol) in EtOH (5 mL) was added skeletal (Raney) nickel catalyst slurry (100 mg) at room temperature. The reaction mixture was stirred under a hydrogen atmosphere for 10 h, diluted with CH_2Cl_2 (50 mL), dried over anhydrous $MgSO_4$, filtered on Celite, and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 11% EtOAc in hexane to give (−)-centrolobine as a syrup (28 mg, 95%): R_f = 0.60 (*n*-hexane–EtOAc = 2:1); $[\alpha]_D^{27} = -89.3$ (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 5.14 (s, 1H), 4.29 (dd, J = 2.0, 11.2 Hz, 1H), 3.78 (s, 3H), 3.44 (m, 1H), 2.67 (m, 2H), 1.95–1.20 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 153.5, 135.7, 134.5, 129.5, 127.2, 115.1, 113.6, 79.2, 77.3, 55.3, 38.2, 33.2, 31.2, 30.7, 24.0; IR (NaCl) ν 2934, 2856, 1613, 1514, 1454, 1246; HRMS (FAB) calcd for $C_{20}H_{24}O_3$ (M^+) 312.1725, observed 312.1721.

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