JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Stereoselective Construction of 2,6-*cis*-Disubstituted Tetrahydropyrans via Intramolecular Amide Enolate Alkylation: Total Synthesis of (−)-Centrolobine

Muhammad Latif,[†,‡] Jeong In Yun,[†] Kalapati Seshadri,[§] Hyoung Rae Kim,[†] Chi Hoon Park,[†] Haeil Park,[§] Hyoungsu Kim,[∥] and Jongkook Lee*[,†,§]

[†]Bio-Organic Science Division, Korea Research Institute of Chemical Technology, PO Box 107, Yuseong, Daejeon 305-600, Republic of Korea

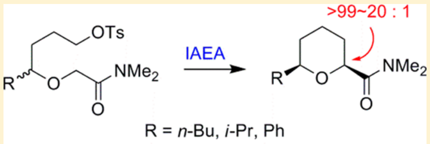
[‡]Korea University of Science and Technology, Daejeon 305-600, Republic of Korea

[§]College of Pharmacy, Kangwon National University, 1 Kangwondaehak-gil, Chuncheon, Gangwon-do 200-701, Republic of Korea

[∥]College of Pharmacy, Ajou University, Suwon, Gyeonggi-do 443-749, Republic of Korea

S *Supporting Information*

ABSTRACT: A highly stereoselective construction of 2,6-*cis*-disubstituted tetrahydropyrans was achieved by using an intramolecular amide enolate alkylation with KHMDS. The efficiency and practicality of this methodology was successfully demonstrated in the total synthesis of (−)-centrolobine (**1**).

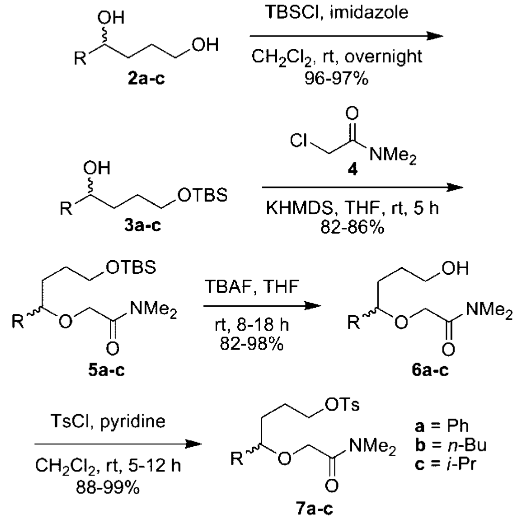


2,6-*cis*-Disubstituted tetrahydropyran (THP) ring systems constitute key structural features in a wide range of biologically active natural products such as SCH 351448,[1] chamuvarinin,[2] and centrolobine (**1**).[3] Although several strategies have been developed for the construction of 2,6-*cis*-disubstituted THPs,[4−6] there is still a need for an efficient, highly stereoselective and high yielding approach to this core unit.

Intramolecular enolate alkylation has frequently been utilized for the synthesis of natural products that contain small carbocycles, tetrahydrofurans, and medium-ring oxacycles,[7] but no reports have yet appeared wherein this methodology was employed to construct THP moieties in natural products. Only a few substituted THP systems have been synthesized by utilizing intramolecular enolate alkylation.[8−11] When α-alkoxyesters were treated with LDA, substituted THPs were generated in moderate to good yield, except for a 2,6-disubstituted case. Contrary to 2,2,6-trisubstituted THP systems, the efficient generation of 2,6-disubstituted THPs was elusive, even in the presence of HMPA.[8] We considered that the poor conversion could be attributed to instability of the ester enolate, and that this problem might be overcome by replacing the ester group with an amide, since amide enolates have been more stable than ester enolates in our experience. We report herein the feasibility of using intramolecular amide enolate alkylation (IAEA) for the construction of 2,6-*cis*-disubstituted THP systems, with particular emphasis on the stereochemical outcome. This report also describes a total synthesis of (−)-centrolobine (**1**), which demonstrates the practicality of IAEA.

Our study commenced with the preparation of IAEA substrates bearing an α-alkoxy amide group, as shown in Scheme 1. Readily available diol **2a** was regioselectively protected with TBSCl to give **3a** in 97% yield.[12] Williamson ether synthesis of alcohol **3a** with α-chloroacetamide **4** provided α-alkoxyamide **5a** in 85% yield. Desilylation of **5a** with TBAF gave alcohol **6a**, which was converted to tosylate **7a** in 97% overall yield. In contrast to the reported ester enolate cyclization,[8] tosylate **7a** with an α-alkoxyamide group underwent a smooth cyclization upon treatment with LDA for 18 h at −30 °C to afford 2,6-*cis*-disubstituted THP ***cis*-8a** as the major component along with diastereomeric ***trans*-8a** in a 6:1 ratio in total 55% yield (Table 1, entry 1). To improve the reaction

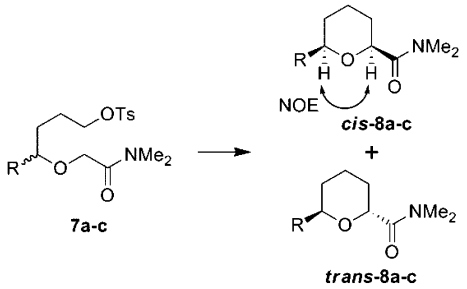
Scheme 1. Synthesis of IAEA Substrates



Received: January 8, 2015
Published: February 27, 2015

DOI: 10.1021/acs.joc.5b00046
J. Org. Chem. 2015, 80, 3315−3320

Table 1. Intramolecular Amide Enolate Alkylation for 2,6-*cis*-Disubstituted Tetrahydropyrans



entry	R	base	solvent	reaction time (h)[a]	yield (%)	ratio[b] *cis*/*trans*
1	**7a** Ph	LDA (1.1 equiv)	THF	18	**8a**, 55	6:1
2	**7a** Ph	LiHMDS (1.1 equiv)	THF	26	**8a**, 96	3:1
3	**7a** Ph	NaHMDS (1.1 equiv)	THF	22	**8a**, 81	3:1
4	**7a** Ph	KHMDS (1.1 equiv)	THF	11	**8a**, 86	20:1
5	**7a** Ph	LiHMDS (1.1 equiv)	THF[c]	11	**8a**, 85	10:1
6	**7a** Ph	KHMDS (1.1 equiv)	THF[c]	11	**8a**, 63	8:1
7	**7a** Ph	KHMDS (3.0 equiv)	THF	9	**8a**, 73	11:1
8	**7a** Ph	KHMDS (1.1 equiv)	ether	11	**8a**, 70	8:1
9	**7a** Ph	KHMDS (1.1 equiv)	DME	13	**8a**, 67	13:1
10	**7a** Ph	KHMDS (1.1 equiv)	toluene	18	**8a**, 66	10:1
11	**7b** *n*-Bu	KHMDS (1.1 equiv)	THF	11	**8b**, 98	>99:1
12	**7c** *i*-Pr	KHMDS (1.1 equiv)	THF	8	**8c**, 88	>99:1

[a] Intramolecular amide enolate alkylation substrates **7a−c** were treated with bases at −78 °C for 5 min, and the reaction mixtures were stirred at −30 °C until the **7a−c** were not detected by TLC. [b] Determined by the analysis of ^1H 500 MHz NMR spectra. [c] The reaction was carried out in the presence of HMPA (5.0 equiv).

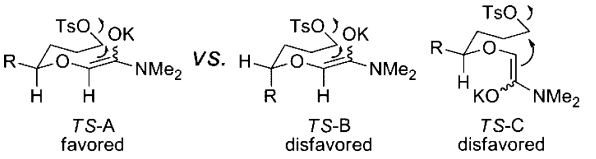


Figure 1. Proposed transition states of IAEA for **8a−c** (the mirror image of *TS*-B is shown for comparison of the transition states).

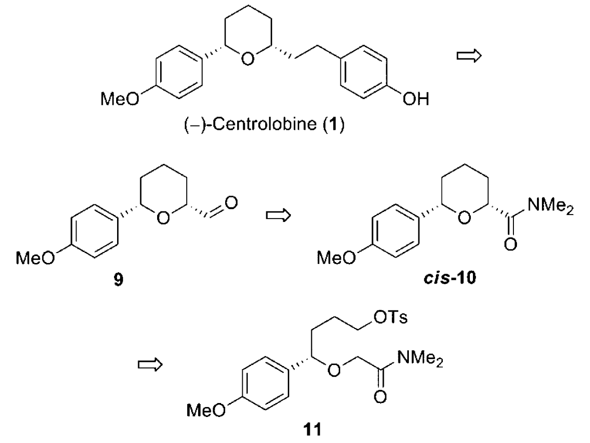
yield and stereoselectivity, we investigated several other bases and solvents.

When LiHMDS or NaHMDS was used instead of LDA, the reaction yield improved to a great extent but the stereoselectivity decreased (Table 1, entries 2 and 3). However, THP ***cis*-8a** was produced with excellent stereoselectivity (*cis*/*trans*, 20:1) in high yield when tosylate **7a** in THF was treated with potassium bis(trimethylsilyl)amide (KHMDS) (Table 1, entry 4). The cyclization was also attempted in the presence of HMPA to improve the reaction, but in vain (Table 1, entries 5 and 6). The results suggest that adequate coordination of metal ions with enolates is essential for high stereoselectivity. Treatment of tosylate **7a** with an excess of KHMDS decreased both the reaction yield and the stereoselectivity (Table 1, entry 7). IAEA of tosylate **7a** with KHMDS was also performed in other solvents, but neither the yield nor the stereoselectivity for this cyclization improved (Table 1, entries 8−10). The relative stereochemistry of the cyclized products ***trans*-8a** and ***cis*-8a** was elucidated through analysis of the NOESY spectra. Tosylates **7b,c** were also prepared from the corresponding diols **2b,c**[13] following the same procedure as for **7a**. When these substrates **7b,c** were subjected to IAEA with KHMDS as a base, ***cis*-8b,c** were also obtained with excellent stereoselectivity in high yield, respectively (Table 1, entries 11 and 12). The observed stereoselectivity can be best rationalized by considering that the reaction proceeds via the folding and allylic strain-controlled[14] chairlike transition state geometry *TS*-A in which the nucleophilic amide enolate moiety assumes an "*H-eclipsed*" conformation with the bulky R group in an equatorial position, to afford a 2,6-*cis*-disubstituted THP product (Figure 1). The high *cis* stereoselectivity of the IAEA is also quite surprising compared to the precedent of intramolecular ester enolate alkylation for the construction of 2,6-substituted THPs, although other appendages on these THP systems might affect the stereoselectivity to some extent. Treatment of an α-alkoxyester of 1,2,5,6-di-*O*-isopropylidene-α-D-allofuranose with LDA produced a 2,6-substituted tetrahydropyran as a mixture of isomers with poor stereoselectivity (*cis*/*trans*, ca. 54:30) in moderate yield.[9] The 2,6-*trans*-substituted tetrahydropyran moiety of 2-deoxy-β-KDO was specifically generated via internal ester enolate S_N2 alkylation.[10]

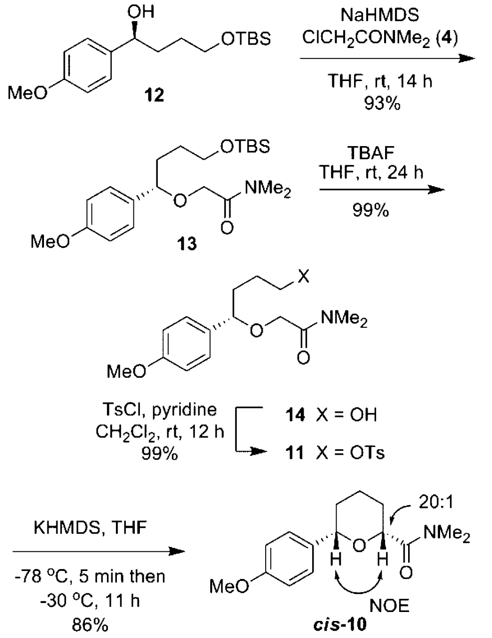
We then turned our attention to the asymmetric total synthesis of a natural product, (−)-centrolobine (**1**),[6] to prove the synthetic utility of this methodology. In spite of its relatively simple chemical structure, (−)-centrolobine (**1**) and related compounds have attracted considerable attention due to their diverse bioactivity, including anti-inflammatory, antibacterial, and antileishmanial properties.[3,15] We envisioned that the THP ***cis*-10**, a precursor of the well-known key intermediate **9**[6a,c] for the synthesis of **1**, could be constructed from tosylate **11** using IAEA. The requisite IAEA substrate **11** was prepared from readily available chiral alcohol **12**,[6e,r] as outlined in Scheme 2.

Williamson etherification of alcohol **12** led to the formation of α-alkoxyamide **13** in 93% yield (Scheme 3). The silyl group in α-alkoxyamide **13** was removed, and the resulting alcohol **14** was transformed into tosylate **11** in 98% overall yield. Treatment of tosylate **11** with KHMDS smoothly produced the 2,6-*cis*-disubstituted THP ***cis*-10** and its diastereomer ***trans*-**

Scheme 2. Retrosynthetic Analysis for (−)-Centrolobine (1)



Scheme 3. Synthesis of Tetrahydropyran Moiety of (−)-Centrolobine (1)

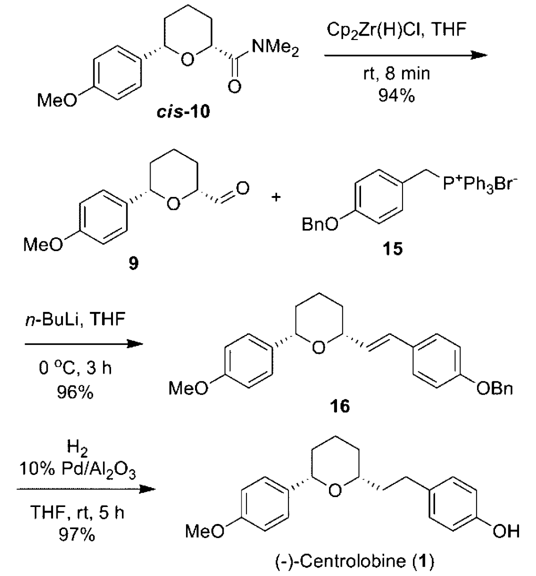


10 in a 20:1 ratio in 86% yield. The stereochemistry of ***cis*-10** and ***trans*-10** was also established by NOE experiments.

With the amide ***cis*-10** in hand, we next sought to complete the synthesis of (−)-centrolobine (**1**), and reduction to aldehyde **9** by hydrozirconation with Schwartz's reagent proceeded in 94% yield (Scheme 4).[16] Aldehyde **9** was transformed into (−)-centrolobine (**1**) following a reported procedure,[6a,c] wherein Wittig reaction of aldehyde **9** with the ylide generated from phosphonium salt **15** afforded olefin **16** in 96% yield. Simultaneous hydrogenation of the alkene moiety and hydrogenolysis of benzyl ether **16** produced (−)-centrolobine (**1**) in 97% yield. The spectral data for (−)-centrolobine (**1**) thus obtained were in good agreement with the reported values.[6c]

In summary, we have demonstrated that IAEA is a viable method for the construction of 2,6-*cis*-disubstituted THP systems with excellent stereoselectivity in excellent yield. The efficiency and practicality of this strategy was also proven by accomplishing an asymmetric total synthesis of (−)-centrolobine (**1**) from readily available alcohol **12** in 7 steps in 65% overall yield. The present strategy can serve as a practical alternative to the existing approaches to 2,6-*cis*-disubstituted THP units in natural products.

Scheme 4. Completion of (−)-Centrolobine (1) Synthesis



■ EXPERIMENTAL SECTION

6-((*t*-Butyldimethylsilyl)oxy)-2-methylhexan-3-ol (3c). To a solution of diol **2c** (100 mg, 0.76 mmol) and imidazole (130 mg, 1.9 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added a solution of TBSCl (140 mg, 0.91 mmol) in anhydrous CH_2Cl_2 (1.0 mL) at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl and concentrated at reduced pressure. The resulting residue was diluted with water and extracted with EtOAc thrice. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 5:1) to give alcohol **3c** (180 mg, colorless oil) in 96% yield: ^1H NMR ($CDCl_3$, 500 MHz) δ 3.70–3.55 (m, 2H), 3.40–3.30 (m, 1H), 2.38 (d, J = 4.5 Hz, 1H), 1.70–1.55 (m, 4H), 1.47–1.39 (m, 1H), 1.01–0.86 (m, 15H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 76.5, 63.7, 33.7, 31.3, 29.5, 26.1, 18.9, 18.5, 17.7, −5.2; HRMS (EI, magnetic sector) m/z calcd for $C_{13}H_{30}O_2Si$ (M^+) 246.2015, found 246.2010.

General Procedure for Williamson Ether Synthesis of 3a–c (GP1). To a solution of alcohol **3a** (100 mg, 0.36 mmol) in anhydrous THF (1.0 mL) was added KHMDS (1.0 mL, 0.50 mmol, 0.5 M solution in THF) at 0 °C. The solution was stirred for 5 min at room temperature. To the solution was added 2-chloro-*N*,*N*-dimethylacetamide (**4**) (56 μL, 0.54 mmol) at 0 °C. The mixture was stirred for 5 h at room temperature. The mixture was quenched with saturated aqueous NH_4Cl and concentrated at reduced pressure. The residue was diluted with water and extracted with EtOAc thrice. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 5:1) to give amide **5a** (111 mg, yellow oil) in 85% yield.

2-(4-((*t*-Butyldimethylsilyl)oxy)-1-phenylbutoxy))-*N*,*N*-dimethylacetamide (5a). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.30 (m, 5H), 4.38 (t, J = 6.8 Hz, 1H), 4.06 (d, J = 13.3 Hz, 1H), 3.91 (d, J = 13.3 Hz, 1H), 3.65–3.57 (m, 2H), 2.95 (s, 3H), 2.93 (s, 3H), 1.99–1.92 (m, 1H), 1.82–1.75 (m, 1H), 1.70–1.64 (m, 1H), 1.54–1.46 (m, 1H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 141.5, 128.4, 127.8, 127.0, 82.7, 67.8, 62.9, 36.5, 35.4, 34.2, 29.0, 26.0, 18.3, −5.3; HRMS (EI, magnetic sector) m/z calcd for $C_{20}H_{35}NO_3Si$ (M^+) 365.2386, found 365.2379.

2-((1-((*t*-Butyldimethylsilyl)oxy)octan-4-yl)oxy))-*N*,*N*-dimethylacetamide (5b). According to **GP1**, **5b** (108 mg, pale yellow oil) was prepared from **3b** in 82% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.12 (s, 2H), 3.63 (s, 2H), 3.42 (t, *J* = 5.0 Hz, 1H), 3.05 (s, 3H), 2.94 (s, 3H), 1.68−1.42 (m, 6H), 1.38−1.20 (m, 4H), 0.91 (s, 12H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 80.2, 68.8, 63.3, 37.0, 35.6, 33.2, 31.1, 29.6, 28.5. 27.5, 26.1, 23.0, 18.5, 14.2, −5.1; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{18}H_{39}NO_3Si$ (M^+) 345.2699, found 345.2697.

2-((6-((*t*-Butyldimethylsilyl)oxy)-2-methylhexan-3-yl)oxy)-*N*,*N*-dimethylacetamide (5c). According to **GP1**, **5c** (117 mg, pale yellow oil) was prepared from **3c** in 86% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.13 (s, 2H), 3.67−3.50 (m, 2H), 3.16 (dd, *J* = 6.5, 11.0 Hz, 1H), 3.07 (s, 3H), 2.94 (s, 3H), 1.89 (dd, *J* = 6.5, 12.5 Hz, 1H), 1.70−1.40 (m, 4H), 0.98−0.80 (m, 15H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 85.5, 69.7, 63.4, 37.1, 35.5, 30.3, 28.9, 26.1, 18.5, 18.4, 17.9, −5.1; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{17}H_{37}NO_3Si$ (M^+) 331.2543, found 331.2547.

General Procedure for Deprotection of Silyl Ether 5a−c (GP2). To a solution of silyl ether **5a** (3.81 g, 10.4 mmol) in anhydrous THF (52 mL) was added TBAF (11.9 mL, 11.9 mmol, 1.0 M solution in THF) at 0 °C. The mixture was stirred for 6 h at room temperature and concentrated at reduced pressure. The resulting residue was dissolved in EtOAc. The solution was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1:1) to give alcohol **6a** (2.51 g, colorless oil) in 98% yield.

2-(4-Hydroxy-1-phenylbutoxy)-*N*,*N*-dimethylacetamide (6a). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.31 (m, 5H), 4.49 (dd, *J* = 8.3, 4.3 Hz, 1H), 4.12 (d, *J* = 13.9, 1H), 3.90 (d, *J* = 14.1, 1H), 3.73−3.68 (m, 2H), 2.94 (s, 3H), 2.88 (s, 3H), 2.42 (brs, 1H), 2.01−1.96 (m, 1H), 1.85−1.71 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 141.6, 128.6, 127.8, 126.8, 82.6, 67.1, 62.8, 36.2, 35.4, 35.2, 29.1; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{14}H_{21}NO_3$ (M^+) 251.1521, found 251.1528.

2-((1-Hydroxyoctan-4-yl)oxy)-*N*,*N*-dimethylacetamide (6b). According to **GP2**, **6b** (81 mg, colorless oil) was prepared from **5b** in 82% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.20 (d, *J* = 13.3 Hz, 1H), 4.09 (d, *J* = 13.3 Hz, 1H), 3.70−3.57 (m, 2H), 3.46−3.41 (m, 1H), 3.03 (s, 3H), 2.94 (s, 3H), 2.21 (brs, 1H), 1.72−1.54 (m, 6H), 1.34−1.25 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 80.4, 68.2, 63.0, 36.7, 35.6, 33.1, 30.0, 28.4, 27.6, 23.0, 14.2; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{12}H_{25}NO_3$ (M^+) 231.1834, found 231.1830.

2-((6-Hydroxy-2-methylhexan-3-yl)oxy)-*N*,*N*-dimethylacetamide (6c). According to **GP2**, **6c** (58 mg, colorless oil) was prepared from **5c** in 89% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.22 (d, *J* = 13.5 Hz, 1H), 4.09 (d, *J* = 13.0 Hz, 1H), 3.73−3.60 (m, 2H), 3.23−3.18 (m, 1H), 3.03 (s, 3H), 2.95 (s, 3H), 2.23 (t, *J* = 6.0 Hz, 1H), 1.93 (ddd, *J* = 6.5, 13.0, 19.0 Hz, 1H), 1.71−1.52 (m, 4H), 0.90 (dd, *J* = 7.0, 17.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 85.9, 69.1, 63.0, 36.8, 35.6, 30.2, 28.9, 26.2, 18.8, 17.6; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{11}H_{23}NO_3$ (M^+) 217.1678, found 217.1676.

General Procedure for Tosylation of Alcohol 6a−c (GP3). To a solution of alcohol **6a** (480 mg, 1.90 mmol) in CH_2Cl_2 (10.0 mL) were added pyridine (3.0 mL) and a solution of *p*-tosyl chloride (656 mg in 4.0 mL anhydrous CH_2Cl_2, 3.43 mmol) at room temperature. The mixture was stirred for 5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with water, and extracted with EtOAc thrice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 4:1) to give tosylate **7a** (745 mg, thick colorless oil) in 99% yield.

4-(2-(Dimethylamino)-2-oxoethoxy)-4-phenylbutyl 4-Methylbenzenesulfonate (7a). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.37−7.26 (m, 7H), 4.38−4.36 (m, 1H), 4.13−4.09 (m, 1H), 4.07−4.03 (m, 2H), 3.87 (d, *J* = 13.2 Hz, 1H), 2.92 (s, 3H), 2.89 (s, 3H), 2.46 (s, 3H), 1.90−1.84 (m, 2H), 1.77−1.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 144.6, 141.0, 133.2, 129.8, 128.5, 128.0, 127.9, 126.8, 81.7, 70.6, 67.1, 36.3, 35.3, 34.0, 25.4, 21.6; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{21}H_{27}NO_5S$ (M^+) 405.1609, found 405.1603.

4-(2-(Dimethylamino)-2-oxoethoxy)octyl 4-Methylbenzenesulfonate (7b). According to **GP3**, **7b** (820 mg, thick colorless oil) was prepared from **6b** in 98% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 4.14−4.04 (m, 4H), 3.37 (quintet, *J* = 5.6 Hz, 1H), 3.03 (s, 3H), 2.95 (s, 3H), 2.47 (s, 3H), 1.83−1.70 (m, 3H), 1.60−1.50 (m, 2H), 1.44−1.40 (m, 1H), 1.33−1.24 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 144.7, 133.2, 129.8, 127.9, 79.4, 70.9, 68.2, 36.6, 35.4, 32.9, 29.3, 27.2, 24.7, 22.8, 21.6, 14.0; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{19}H_{31}NO_5S$ (M^+) 385.1922, found 385.1918.

4-(2-(Dimethylamino)-2-oxoethoxy)-5-methylhexyl 4-Methylbenzenesulfonate (7c). According to **GP3**, **7c** (619 mg, thick colorless oil) was prepared from **6c** in 88% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 4.16−4.02 (m, 4H), 3.15−3.12 (m, 1H), 3.03 (s, 3H), 2.94 (s, 3H), 2.46 (s, 3H), 1.90−1.76 (m, 2H), 1.75−1.64 (m, 2H), 1.54−1.43 (m, 1H), 0.88 (d, *J* = 6.9, Hz, 3H), 0.85 (d, *J* = 6.9, Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 144.7, 133.1, 129.8, 127.9, 84.6, 71.0, 69.0, 36.7, 35.3, 29.9, 25.6, 25.1, 21.6, 18.4, 17.2; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{18}H_{29}NO_5S$ (M^+) 371.1766, found 371.1762.

General Procedure for Cyclization of Tosylate 7a−c (GP4). To a solution of tosylate **7a** (50.0 mg, 0.13 mmol) in anhydrous THF (13.0 mL) was added dropwise KHMDS (0.3 mL, 0.15 mmol, 0.5 M in THF) at −78 °C under a N_2 atmosphere. The mixture was stirred at the same temperature for 5 min. The mixture was warmed to −30 °C immediately and stirred at this temperature for 11 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, and concentrated in vacuo. The residue was diluted with water and extracted with EtOAc thrice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 10:1) to give ***cis*-8a** (24.0 mg, colorless oil, 82%) along with ***trans*-8a** (1.2 mg, colorless oil, 4%).

THP 8a. Data for ***cis*-8a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.34 (m, 4H), 7.30−7.28 (m, 1H), 4.45 (dd, *J* = 11.3, 1.6 Hz, 1H), 4.30 (dd, *J* = 11.1, 2.4 Hz, 1H), 3.13 (s, 3H), 2.97 (s, 3H), 2.10−2.07 (m, 1H), 1.96−1.69 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 142.6, 128.3, 127.4, 125.8, 80.6, 77.3, 37.1, 35.9, 33.3, 26.9, 23.5; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{14}H_{19}NO_2$ (M^+) 233.1415, found 233.1414. Data for ***trans*-8a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.35 (m, 4H), 7.30−7.29 (m, 1H), 4.77−4.73 (m, 1H), 4.54 (dd, *J* = 10.8, 2.2 Hz, 1H), 3.11 (s, 3H), 3.00 (s, 3H), 2.10−2.07 (m, 1H), 1.96−1.69 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 142.9, 128.3, 127.3, 125.9, 75.2, 72.0, 37.6, 35.9, 32.7, 25.6, 20.0; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{14}H_{19}NO_2$ (M^+) 233.1415, found 233.1416.

THP *cis*-8b. According to **GP4**, ***cis*-8b** (47 mg, colorless oil) was prepared from **7b** in 95% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.06 (dd, *J* = 10.6, 2.9 Hz, 1H), 3.38−3.32 (m, 1H), 3.11 (s, 3H), 2.97 (s, 3H), 1.98−1.92 (m, 1H), 1.82−1.70 (m, 2H), 1.63−1.49 (m, 4H), 1.47−1.41 (m, 2H), 1.37−1.25 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 79.9, 76.4, 37.0, 36.1, 35.7, 31.3, 27.9, 27.2, 23.1, 22.7, 14.0; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{12}H_{23}NO_2$ (M^+) 213.1728, found 213.1724. The expected minor product ***trans*-8b** could not be isolated.

THP *cis*-8c. According to **GP4**, ***cis*-8c** (45 mg, colorless oil) was prepared from **7c** in 88% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.04 (dd, *J* = 11.2, 2.4 Hz, 1H), 3.11 (s, 3H), 3.07−3.03 (m, 1H), 2.96 (s, 3H), 1.99−1.95 (m, 1H), 1.80−1.63 (m, 5H), 1.32−1.24 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 84.1, 76.6, 37.0, 35.7, 33.3, 28.1, 27.2, 23.1, 18.8, 18.7; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{11}H_{21}NO_2$ (M^+) 199.1572, found 199.1569. The expected minor product ***trans*-8c** could not be isolated.

(*S*)-2-(4-((*t*-Butyldimethylsilyl)oxy)-1-(4-methoxyphenyl)butoxy)-*N*,*N*-dimethylacetamide (13). To a solution of alcohol **12** (523 mg, 1.68 mmol) in THF (6.0 mL) at room temperature was added NaHMDS (1.0 M solution in THF, 2.5 mL, 2.52 mmol). The mixture was stirred for 10 min. To the mixture was added 2-chloro-N,N-dimethylacetamide (4) (259 μL, 2.52 mmol). The mixture was stirred for 14 h at 40 °C, quenched with saturated aqueous NH_4Cl and concentrated at reduced pressure. The residue was diluted with water and extracted with EtOAc thrice. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 7:2) to give amide **13** (589 mg, thick colorless oil) in 93% yield: $[\alpha]^{20}_{\mathrm{D}}$ = −49.5 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.32 (t, J = 6.7 Hz, 1H), 4.02 (d, J = 13.5 Hz, 1H), 3.88 (d, J = 13.1 Hz, 1H), 3.82 (s, 3H), 3.56−3.64 (m, 2H), 2.94 (s, 3H), 2.92 (s, 3H), 1.98−1.91 (m, 1H), 1.79−1.72 (m, 1H), 1.69−1.61 (m, 1H), 1.49−1.43 (m, 1H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 159.2, 133.4, 128.3, 113.8, 82.2, 67.6, 63.0, 55.3, 36.6, 35.4, 34.1, 29.1, 26.0, 18.3, −5.3; HRMS (EI, magnetic sector) m/z calcd for $C_{21}H_{37}NO_4Si$ (M^+) 395.2491, found 395.2499.

(S)-2-(4-Hydroxy-1-(4-methoxyphenyl)butoxy)-N,N-dimethylacetamide (14). To a solution of silyl ether **13** (3.10 g, 7.84 mmol) in anhydrous THF (26.0 mL) was added TBAF (9.4 mL, 9.4 mmol, 1.0 M solution in THF) at room temperature. The mixture was stirred for 24 h and filtered through a pad of Celite. The filtrate was concentrated at reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1:1) to give alcohol **14** (2.20 g, thick pale yellow oil) in 99% yield: $[\alpha]^{20}_{\mathrm{D}}$ = −94.1 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28 (s, 1H), 7.25 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.45−4.42 (m, 1H), 4.08 (d, J = 13.9 Hz, 1H), 3.88 (d, J = 13.9 Hz, 1H), 3.83 (s, 3H), 3.72−3.66 (m, 2H), 2.93 (s, 3H), 2.88 (s, 3H), 2.39 (brs, 1H), 2.02−1.95 (m, 1H), 1.81−1.69 (m, 2H): ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 159.2, 133.5, 128.1, 113.9, 82.1, 66.8, 62.9, 55.3, 36.2, 35.4, 35.1, 29.2; HRMS (EI, magnetic sector) m/z calcd for $C_{15}H_{23}NO_4$ (M^+) 281.1627, found 281.1625.

(S)-4-(2-(Dimethylamino)-2-oxoethoxy)-4-(4-methoxyphenyl)butyl 4-Methylbenzenesulfonate (11). To a stirred solution of alcohol **14** (850 mg, 3.02 mmol) in CH_2Cl_2 (15 mL) at room temperature were added pyridine (4.6 mL, 57.39 mmol) and a solution of p-tosyl chloride (922 mg in 4.0 mL of CH_2Cl_2, 4.83 mmol). The reaction mixture was stirred for 12 h at room temperature, and quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with water, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 thrice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 8:2) to give tosylate **11** (1301 mg, thick colorless oil) in 99% yield: $[\alpha]^{20}_{\mathrm{D}}$ = −61.6 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, J = 7.4 Hz, 2H), 7.34 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.33−4.29 (m, 1H), 4.12−4.00 (m, 3H), 3.84 (d, J = 13.1 Hz, 1H), 3.83 (s, 3H), 2.92 (s, 3H), 2.89 (s, 3H), 2.46 (s, 3H), 1.90−1.83 (m, 2H), 1.75−1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 159.4, 144.6, 133.1, 132.9, 129.8, 128.1, 127.9, 114.0, 81.2, 70.6, 66.9, 55.3, 36.3, 35.3, 33.9, 25.5, 21.6; HRMS (EI, magnetic sector) m/z calcd for $C_{22}H_{29}NO_6S$ (M^+) 435.1715, found 435.1711.

Cyclization of Tosylate 11. KHMDS (0.2 mL, 0.19 mmol, 1.0 M in THF) was added to a solution of **11** (75.0 mg, 0.17 mmol) in anhydrous THF (17.0 mL) under a N_2 atmosphere at −78 °C. The mixture was stirred for 30 min at the same temperature and for 11 h at −30 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl, and concentrated in vacuo. The residue was diluted with water and extracted with EtOAc thrice. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 10:1) to afford a mixture of ***cis*-10** (40 mg, colorless thick oil, 82%) and ***trans*-10** (2.0 mg, colorless thick oil, 4%). Data for ***cis*-10a**: $[\alpha]^{20}_{\mathrm{D}}$ = −31.0 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.2 Hz, 2H), 4.39 (dd, J = 10.9, 1.9 Hz, 1H), 4.28 (dd, J = 11.9, 2.3 Hz, 1H), 3.80 (s, 3H), 3.13 (s, 3H), 2.96 (s, 3H), 2.08−2.10 (m, 1H), 1.94−1.62 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 159.0, 134.8, 127.2, 113.7, 80.4, 77.3, 55.3, 37.1, 35.9, 33.1, 26.9, 23.5; HRMS (EI, magnetic sector) m/z calcd for $C_{15}H_{21}NO_3$ (M^+) 263.1521, found 263.1526. Data for ***trans*-10a**: $[\alpha]^{20}_{\mathrm{D}}$ = −60.0 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28 (d, J = 8.3 H, 2H), 6.89 (d, J = 8.3 Hz, 2H), 4.73−4.70 (m, 1H), 4.48 (d, J = 10.8 Hz, 1H), 3.82 (s, 3H), 3.10 (s, 3H), 3.01 (s, 3H), 2.22−2.12 (m, 2H), 1.86−1.66 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 158.9, 135.0, 127.3, 113.7, 74.9, 72.0, 55.3, 37.7, 35.9, 32.4, 25.6, 20.0; HRMS (EI, magnetic sector) m/z calcd for $C_{15}H_{21}NO_3$ (M^+) 263.1521, found 263.1520.

(2S,6R)-2-(p-Methoxyphenyl)-6-formyltetrahydropyran (9). To a homogeneous solution of $Cp_2Zr(H)Cl$ (235 mg, 0.91 mmol) in THF (5.0 mL) was added ***cis*-10** (200 mg, 0.76 mmol) in THF (4.0 mL) at room temperature, and the mixture was stirred for 8 min. The reaction mixture was quenched with silica gel and filtered through a short pad of silica gel. The filtrate was concentrated in vacuo to afford aldehyde **9** (157 mg, colorless oil) in 94% yield: $[\alpha]^{20}_{\mathrm{D}}$ = −9.1 (c 3.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.73 (s, 1H), 7.35 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 4.45 (dd, J = 11.1, 1.7 Hz, 1H), 4.48 (dd, J = 10.8 Hz, 2.3 Hz, 1H), 3.83 (s, 3H), 2.10−2.06 (m, 1H), 1.95−1.86 (m, 2H), 1.80−1.71 (m, 1H), 1.67−1.58 (m, 1H), 1.52−1.43 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.3, 159.2, 134.4, 127.2, 113.8, 82.2, 79.7, 55.3, 33.1, 26.0, 23.3; HRMS (EI, magnetic sector) m/z calcd for $C_{13}H_{16}O_3$ (M^+) 220.1099, found 220.1104.

(2S,6R)-6-[(p-Benzyloxyphenyl)vinyl]-2-(p-methoxyphenyl)-tetrahydropyran (16). To a solution of phosphonium salt **15** (804 mg, 1.49 mmol) in THF (17.0 mL) at 0 °C was added n-BuLi (1.5 mL, 0.93 mmol, 1.6 M solution in hexanes). The mixture was stirred for 15 min at 0 °C. A solution of aldehyde **9** (164 mg, 0.75 mmol) in THF (8.0 mL) was added to the mixture. The mixture was stirred at 0 °C for 30 min, and silica gel was added. The mixture was stirred for 15 min at room temperature and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 5:1) to afford olefin **16** (287 mg, white solid) in 96% yield as an E/Z (1:3.6, ^1H 500 MHz NMR analysis) mixture: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48−7.30 (m, 9H), 6.99−6.89 (m, 4H), 6.59 (d, J = 15.6 Hz, 1H), 6.52 (d, J = 11.6 Hz, 1H), 6.19 (dd, J = 15.9, 5.9 Hz, 1H), 5.69 (dd, J = 11.5, 8.6 Hz, 1H), 5.10 (s, 2H), 5.08 (s, 2H) 4.47−4.41 (m, 1H), 4.21−4.21 (m, 1H), 3.82 (s, 3H), 2.10−1.90 (m, 1H), 1.86−1.55 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.9, 158.3, 158.0, 137.0, 135.6, 135.5, 131.6, 130.8, 130.2, 129.9, 129.3, 129.0, 128.7, 128.6, 128.0, 127.9, 127.6, 127.5, 127.4, 127.3, 114.8, 114.6, 113.7, 79.6, 79.0, 78.8, 77.3, 74.9, 70.0, 55.3, 33.4, 32.8, 31.7, 31.5, 24.1, 23.9; HRMS (EI, magnetic sector) m/z calcd for $C_{27}H_{28}O_3$ (M^+) 400.2038, found 400.2032.

(−)-Centrolobine (1). A mixture of olefin **16** (40 mg, 0.09 mmol) and Pd/Al_2O_3 (60 mg) in THF (4.0 mL) was stirred for 5 h under a hydrogen atmosphere at room temperature. The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated, and the resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1:1) to afford (−)-centrolobine (**1**) (30 mg, white solid) in 97% yield: $[\alpha]^{20}_{\mathrm{D}}$ = −94.5 (c 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 8.2 Hz, 2H), 4.70 (s, 1H), 4.32 (dd, J = 11.1, 1.3 Hz, 1H), 3.83 (s, 3H), 4.49−3.44 (m, 1H), 2.78−2.65 (m, 2H), 1.98−1.84 (m, 3H), 1.78−1.69 (m, 1H), 1.68−1.61 (m, 2H), 1.57−1.49 (m, 1H), 1.40−1.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 153.4, 135.9, 134.7, 129.6, 127.1, 115.1, 113.6, 79.1, 77.2, 55.3, 38.3, 33.3, 31.3, 30.8, 24.1; HRMS (EI, magnetic sector) m/z calcd for $C_{20}H_{24}O_3$ (M^+) 312.1725, found 312.1721.

ASSOCIATED CONTENT

Supporting Information

Copies of the ^1H and ^{13}C NMR spectra for all new compounds and **9**, **16**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jkl@kangwon.ac.kr (J.L.).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by a 2012 Research Grant from Kangwon National University, and the Basic Science Research Program and the Bio & Medical Technology Development Program through the National Research Foundation of Korea (NRF) grant funded by the Ministry of Science, ICT & Future Planning (NRF-2012R1A1A1038686 and NRF-2012M3A9A9054971). We thank Professor Deukjoon Kim (Seoul National University) for his helpful advice on IAEA and the Central Laboratory of Kangwon National University for providing us with technical assistance on the spectroscopic experiments.

DEDICATION

This work was dedicated to Professor Deukjoon Kim on the occasion of his 66th birthday.

REFERENCES

(1) Hegde, V. R.; Puar, M. S.; Dai, P.; Patel, M.; Gullo, V. P.; Das, P. R.; Bond, R. W.; McPhail, A. T. *Tetrahedron Lett.* **2000**, *41*, 1351.

(2) (a) Fall, D.; Duval, R. A.; Gleye, C.; Laurens, A.; Hocquemiller, R. *J. Nat. Prod.* **2004**, *67*, 1041. (b) Florence, G. J.; Morris, J. C.; Murray, R. G.; Osler, J. D.; Reddy, V. R.; Smith, T. K. *Org. Lett.* **2011**, *13*, 514. (c) Florence, G. J.; Morris, J. C.; Murray, R. G.; Vanga, R. R.; Osler, J. D.; Smith, T. K. *Chem.—Eur. J.* **2013**, *19*, 8309.

(3) (a) De Albuquerque, I. L.; Galeffi, C.; Casinovi, C. G.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1964**, 287. (b) Galeffi, C.; Casinovi, C. G.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1965**, 95. (c) Arango Craveiro, A.; da Costa Prado, A.; Gottlieb, O. R.; Welerson de Albuquerque, P. C. *Phytochemistry* **1970**, *9*, 1869. (d) Jurd, L.; Wong, R. Y. *Aust. J. Chem.* **1984**, *37*, 1127. (e) de C. Alcantara, A. F.; Souza, M. R.; Piló-Veloso, D. *Fitoterapia* **2000**, *71*, 613.

(4) For some recent examples, see: (a) Gharpure, S. J.; Prasad, J. V. K.; Bera, K. *Eur. J. Org. Chem.* **2014**, 3570. (b) Dai, Q.; Rana, N. K.; Zhao, J. C.-G. *Org. Lett.* **2013**, *15*, 2922. (c) Kim, Y. S.; Lee, J. K.; Pae, A. N.; Cho, Y. S.; Min, S.-J. *Synlett* **2013**, *24*, 2292. (d) Fuwa, H.; Noguchi, T.; Noto, K.; Sasaki, M. *Org. Biomol. Chem.* **2012**, *10*, 8108. (e) Fuwa, H.; Ichinokawa, N.; Noto, K.; Sasaki, M. *J. Org. Chem.* **2012**, *77*, 2588. (f) Guérinot, A.; Serra-Muns, A.; Bensoussan, C.; Reymond, S.; Cossy, J. *Tetrahedron* **2011**, *67*, 5024. (g) Nagasawa, T.; Nukada, T.; Kuwahara, S. *Tetrahedron* **2011**, *67*, 2882.

(5) For reviews on this subject, see: (a) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348. (b) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045. (c) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683. (d) Smith, A. B., III; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675. (e) Nasir, N. M.; Ermanis, K.; Clarke, P. A. *Org. Biomol. Chem.* **2014**, *12*, 3323.

(6) For reported syntheses of centrolobine, see: (a) Colobert, F.; Mazery, R. D.; Solladié, G.; Carreño, M. C. *Org. Lett.* **2002**, *4*, 1723. (b) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (c) Carreño, M. C.; Mazery, R. D.; Urbano, A.; Colobert, F.; Solladie, G. *J. Org. Chem.* **2003**, *68*, 7779. (d) Evans, P. A.; Cui, J.; Gharpure, S. J. *Org. Lett.* **2003**, *5*, 3883. (e) Lee, E.; Kim, H. J.; Jang, W. S. *Bull. Korean Chem. Soc.* **2004**, *25*, 1609. (f) Boulard, L.; BouzBouz, S.; Cossy, J.; Franck, X.; Figadère, B. *Tetrahedron Lett.* **2004**, *45*, 6603. (g) Clarke, P. A.; Martin, W. H. C. *Tetrahedron Lett.* **2004**, *45*, 9061. (h) Chan, K.-P.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 4491. (i) Clarke, P. A.; Martin, W. H. C. *Tetrahedron* **2005**, *61*, 5433. (j) Jennings, M. P.; Clemens, R. T. *Tetrahedron Lett.* **2005**, *46*, 2021. (k) Chandrasekhar, S.; Prakash, S. J.; Shyamsunder, T. *Tetrahedron Lett.* **2005**, *46*, 6651. (l) Sabitha, G.; Reddy, K. B.; Reddy, G. S. K. K.; Fatima, N.; Yadav, J. S. *Synlett* **2005**, 2347. (m) Böhrsch, V.; Blechert, S. *Chem. Commun.* **2006**, 1968. (n) Lee, C.-H. A.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 1641. (o) Prasad, K. R.; Anbarasan, P. *Tetrahedron* **2007**, *63*, 1089. (p) Washio, T.; Yamaguchi, R.; Abe, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron* **2007**, *63*, 12037. (q) Dziedzic, M.; Furman, B. *Tetrahedron Lett.* **2008**, *49*, 678. (r) Takeuchi, T.; Matsuhashi, M.; Nakata, T. *Tetrahedron Lett.* **2008**, *49*, 6462. (s) Zhou, H.; Loh, T.-P. *Tetrahedron Lett.* **2009**, *50*, 4368. (t) He, A.; Sutivisedsak, N.; Spilling, C. D. *Org. Lett.* **2009**, *11*, 3124. (u) Schmidt, B.; Hölter, F. *Chem.—Eur. J.* **2009**, *15*, 11948. (v) Mohapatra, D. K.; Pal, R.; Rahaman, H.; Gurjar, M. K. *Heterocycles* **2010**, *80*, 219. (w) Chaładaj, W.; Kowalczyk, R.; Jurczak, J. *J. Org. Chem.* **2010**, *75*, 1740. (x) Rogano, F.; Rüedi, P. *Helv. Chim. Acta* **2010**, *93*, 1281. (y) Fuwa, H.; Noto, K.; Sasaki, M. *Heterocycles* **2010**, *82*, 641. (z) Reddy, C. R.; Madhavi, P. P.; Chandrasekhar, S. *Tetrahedron: Asymmetry* **2010**, *21*, 103. (aa) Jeong, Y.; Kim, D.-Y.; Choi, Y.; Ryu, J.-S. *Org. Biomol. Chem.* **2011**, *9*, 374. (ab) Fujioka, H.; Yahata, K.; Kubo, O.; Sawama, Y.; Hamada, T.; Maegawa, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 12232. (ac) Reddy, C. R.; Madhavi, P. P.; Chandrasekhar, S. *Synthesis* **2011**, 123. (ad) Iqbal, M.; Mistry, N.; Clarke, P. A. *Tetrahedron* **2011**, *67*, 4960. (ae) Xie, J.-H.; Guo, L.-C.; Yang, X.-H.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2012**, *14*, 4758. (af) Kumaraswamy, G.; Rambabu, D. *Tetrahedron: Asymmetry* **2013**, *24*, 196. (ag) Sudarshan, K.; Aidhen, I. S. *Eur. J. Org. Chem.* **2013**, 2298. (ah) Zeng, J.; Tan, Y. J.; Ma, J.; Leow, M. L.; Tirtorahardjo, D.; Liu, X.-W. *Chem.—Eur. J.* **2014**, *20*, 405. (ai) Yang, Z.; Kim, H.-D. *Tetrahedron: Asymmetry* **2014**, *25*, 305.

(7) For reviews on this subject, see: (a) Kim, D. *Synlett* **2014**, *25*, 33. (b) Devambatla, R. K. V.; Velagaleti, R.; Yarravarapu, N.; Fleming, F. F. *Tetrahedron* **2012**, *68*, 2925.

(8) (a) Fujisawa, T.; Okumura, Y.; Morita, K.; Ukaji, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3487. (b) The *cis/trans* stereoselectivity of this cyclization reaction was not indicated in this report.

(9) Knapp, S.; Thakur, V. V.; Madduru, M. R.; Malolanarasimhan, K.; Morriello, G. J.; Doss, G. A. *Org. Lett.* **2006**, *8*, 1335.

(10) Ohrui, H.; Morita, M.; Meguro, H. *Carbohydr. Res.* **1992**, *224*, 319.

(11) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2003**, *125*, 10238.

(12) (a) Mullah, K. B.; Bentrude, W. G. *J. Org. Chem.* **1991**, *56*, 7218. (b) Kim, H.; Lee, C. *Org. Lett.* **2011**, *13*, 2050.

(13) (a) Ramu, R.; Chang, C.-W.; Chou, H.-H.; Wu, L.-L.; Chiang, C.-H.; Yu, S. S.-F. *Tetrahedron Lett.* **2011**, *52*, 2950. (b) McDonald, C. E.; Beebe, T. R.; Beard, M.; McMillen, D.; Selski, D. *Tetrahedron Lett.* **1989**, *30*, 4791. (c) Montaudon, E.; Thépénier, J.; Lalande, R. *J. Heterocycl. Chem.* **1979**, *16*, 113.

(14) (a) Tokoroyama, T.; Okada, K.; Iio, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1572. (b) Tokoroyama, T.; Kusaka, H. *Can. J. Chem.* **1996**, *74*, 2487. For a review, see: (c) Tokoroyama, T. *Chem.—Eur. J.* **1998**, *4*, 2397.

(15) Araujo, C. A. C.; Alegrio, L. V.; Leon, L. L. *Phytochemistry* **1998**, *49*, 751.

(16) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408.