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Stereoselective Syntheses of Four Diastereomers of 3,9,12-Trihydroxycalamenene via a Benzobicyclo[3.3.1] Intermediate

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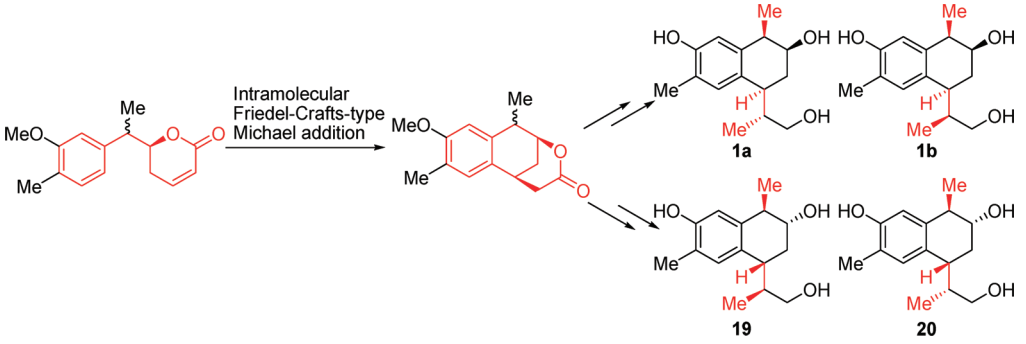

The highly stereoselective syntheses of four diastereomers of natural 3,9,12-trihydroxycalamenene are described. The syntheses highlight the utility of an unusual framework of benzobicyclo[3.3.1] lactones, which were accomplished via an intramolecular Friedel−Crafts-type Michael addition of α,β-unsaturated lactones.

Introduction

Since the late 1990s, a large number of aromatic diterpenes with a serrulatane or amphilectane framework have been isolated from marine soft corals, especially *Pseudopterogorgia elisabethae*. Many members of them exhibit substantial biological activities such as anti-inflammatory, anticancer, antitubercular, and antibacterial agents. The biological activity and commercial potential of the compounds stimulated a number of approaches to their synthesis.[1,2] From a synthetic perspective, a major challenge associated with their syntheses has been the control of the three stereocenters marked in Figure 1, because there are no convenient neighboring functional groups available to assist in their stereocontrol. Therefore, it is very desirable to develop a strategy to the highly stereoselective installation of this array of stereocenters.

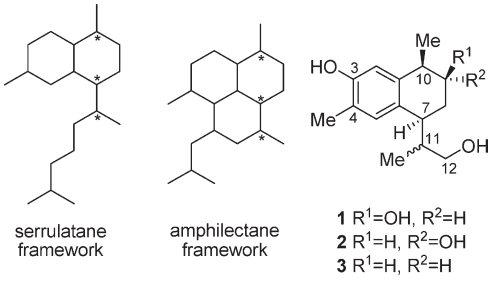

FIGURE 1. Frameworks of serrulatane and amphilectane and structures of **1**, **2**, and **3**.

In 2006, three new aromatic cadinane sesquiterpenes, 3,9,12-trihydroxycalamenenes **1**, **2**, and 3,12-dihydroxycalamenene **3**, were isolated by bioassay-guided fractionation

(1) For a general review on the isolation, synthesis, and biosynthesis of these natrual products, see: (a) Berrue, F.; Kerr, R. G. *Nat. Prod. Rep.* **2009**, *26*, 681. (b) Heckrodt, T. J.; Mulzer, J. *Top. Curr. Chem.* **2005**, *244*, 1.

(2) Some representative examples for the synthesis: (a) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485. (b) Harmata, M.; Hong, X.; Schreiner, P. R. *J. Org. Chem.* **2008**, *73*, 1290. (c) Nicolau, K. C.; Vassilikogiannakis, G.; Magerlein, W.; Kranich, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2482. (d) Boezio, A. A.; Jarvo, E. R.; Lawrence, B. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6046. (e) Johnson, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, *123*, 4475. (f) Chow, R.; Kocienski, P. J.; Kuhl, A.; LeBrazidec, J. Y.; Muir, K.; Fish, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2344. (g) Kocienski, P. J.; Pontiroli, A.; Qun, L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2356. (h) Uemura, M.; Nishimura, H.; Minami, T.; Hayashi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 5402.

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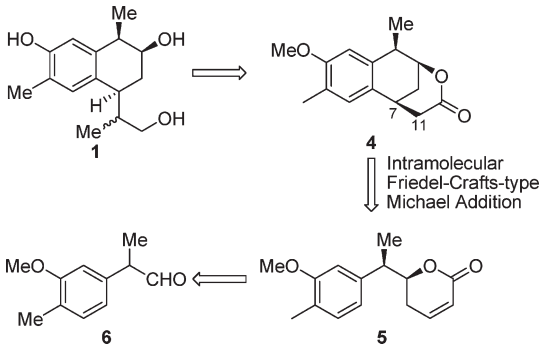
SCHEME 1. Retrosynthetic Analysis of 3,9,12-Trihydroxycalamenene 1

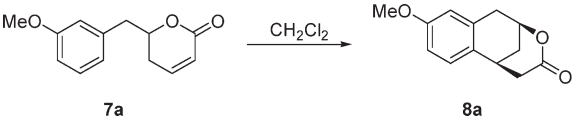


from *Phomopis cassiae*, an endophytic fungus (Figure 1).[3] As new members of important precursors for the synthesis of the diterpenes mentioned above,[2b,e−g] they attracted our interest. The structures of **1** and **2** differ from that of **3** by the presence of a C9-hydroxyl group. Moreover, their undetermined stereochemistry at C11 inspired us to find a common path for the stereoselective installation of the three stereocenters. Herein we report a highly efficient construction of benzobicyclo[3.3.1] framework, and based on this framework, four diastereomers of 3,9,12-trihydroxycalamenene were synthesized.

Results and Discussion

To develop a potentially general and diversity-oriented strategy to the flexible and stereoselective installation of the three stereocenters, the rigid benzobicyclo[3.3.1] lactone[4] was envisioned to be the key intermediate that was expected to be obtained via an intramolecular Friedel−Crafts-type Michael addition of the corresponding α,β-unsaturated lactone. On the basis of this strategy, the retrosynthetic analysis of 3,9,12-trihydroxycalamenene **1** was outlined in Scheme 1. We envisioned that the bridged lactone **4** was a very desirable precursor to **1**, and **4** was expected to be derived from an intramolecular Friedel−Crafts-type Michael addition of α,β-unsaturated lactone **5**. As for the preparation of **5**, it was easily obtained from α-methyl phenyl acetaldehyde **6**.

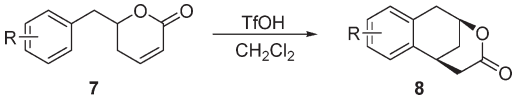
Even though the dual activated α,β-unsaturated compounds easily facilitated the inter- or intramolecular Friedel−Crafts-type Michael addition under Lewis acid conditions,[5] there were few examples of α,β-unsaturated lactones to be applied in the reaction. To test the feasibility, a model reaction was carried out with *m*-methoxy-substituted lactone **7a** as the substrate (eq 1). After several unsuccessful attempts under Lewis acid conditions ($TiCl_4$, $SnCl_4$, F_3B-OEt_2, $AlCl_3$), triflic acid, a strong organic protic acid, was found to be the efficient reagent to promote this reaction, while the relative weaker acids (TsOH, TFA) did not play any role at all. In this process, 2.5 equiv of triflic acid was essential.

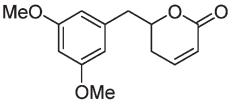
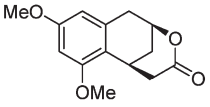
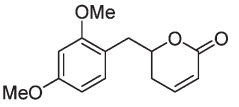
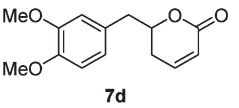
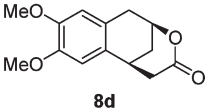
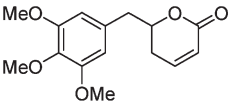
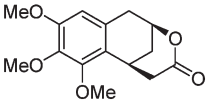
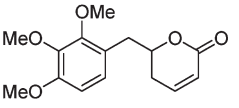
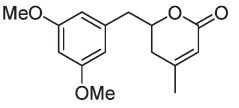
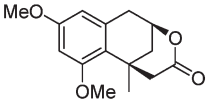
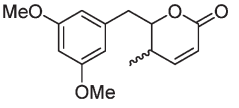
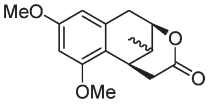


(1)

With the optimized conditions in hand, several substrates were investigated (Table 1). 3,5-Dimethoxy- and

TABLE 1. Examples of Intramolecular Friedel−Crafts-Type Michael Addition of α,β-Unsaturated Lactone 7[a]



entry	substrate	product	yield (%)[b]
1	**7a**	**8a**	72
2[c]	 **7b**	 **8b**	88
3	 **7c**	-	NR[d]
4	 **7d**	 **8d**	62[e]
5	 **7e**	 **8e**	78
6	 **7f**	-	NR[d]
7[c]	 **7g**	 **8g**	92
8[c,f]	 **7h**	 **8h**	81

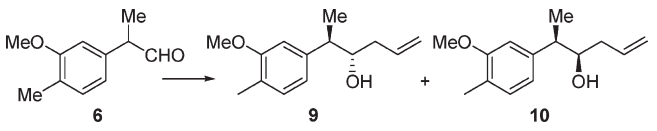
[a]Unless otherwise indicated, all reactions were performed on a 0.5 mmol scale at 0.1 M in CH_2Cl_2 for 24 h at room temperature. [b]Isolated yield. [c]Reaction time: 12 h. [d]Quantitative recovery of the starting material. [e]Isolated yield based on the recovery of 20% of starting material. [f]A 1:1 diastereomeric mixture of **7h** or **8h** was illustrated.

(3) Silva, G. H.; Teles, H. L.; Zanardi., L. M.; Young, M. C. M.; Eberlin, M. N.; Hadad, R.; Pfenning, L. H.; Costa-Neto, C. M.; Castro-Gamboa, I.; Bolzani, V. S.; Araújo, Â. R. *Phytochemistry* **2006**, *67*, 1964.

(4) (a) Williams, D. R.; Ihle, D. C.; Brugel, T. A.; Patnaik, S. *Heterocycles* **2006**, *70*, 77. (b) Kawamura, M.; Ogasawara, K. *Tetrahedron Lett.* **1995**, *36*, 3369. (c) Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1584. (d) Takano, S.; Masuda, K.; Hatakeyama, S.; Ogasawara, K. *Heterocycles* **1982**, *19*, 1407.

(5) (a) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. (b) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739. (c) Liu, H. J.; Tran, D. D. P. *Tetrahedron Lett.* **1999**, *40*, 3827.

SCHEME 2. Allylation of α-Methyl Phenyl Acetaldehyde 6



3,4,5-trimethoxy-substituted substrates (entries 2 and 5) proceeded smoothly under these conditions, while 2,4-dimethoxy- and 2,3,4-trimethoxy-substituted substrates (entries 3 and 6) did not react. This indicated that the methoxy group located at the meta position to the reaction site would reduce the activity of the reaction site, which was not favored for the reaction. This could be confirmed by the reaction of 3,4-dimethoxy-substituted substrates which afforded **8d** in 62% yield (recovery of 20% of **7d**, entry 4). The reaction time was shortened if more electron-donating substituents were attached to the aromatic ring (entries 2, 7, and 8). And to our delight, the substrates **7g** and **7h** could also react well to give the products **8g** and **8h** bearing bridgehead quaternary carbon and bridge methyl group, respectively (entries 7 and 8).

Having established the method to construct the key benzobicyclo[3.3.1] framework, attention was then directed toward the syntheses of 3,9,12-trihydroxycalamenenes, which began with the allylation of the α-methyl aryl acetaldehyde **6** (Scheme 2). Under the cooperation of allylindium sesquibromide and lithium neopentoxide at −78 °C, compound **10** was obtained as the major product (Felkin−Ahn product) in satisfactory diastereoselectivity (8.5:1) and yield (95%).[6] Otherwise, the anti-Felkin−Ahn product **9** was obtained from aldehyde **6** through a three-step sequence in 74% overall yield (allylation,[7] oxidation, and L-Selectride reduction[8]).

The esterification reaction between homoallyl alcohol **9** and acryloyl chloride afforded the ring-closing-metathesis precursor **11** in 93% yield (Scheme 3). Treatment of **11** with Grubbs catalyst first under high dilution in CH_2Cl_2 at reflux furnished the α,β-unsaturated lactone **5** in 86% yield.[9] With **5** in hand, the intramolecular Friedel−Crafts-type Michael addition was executed under the above-mentioned conditions at 0 °C to construct the bridged lactone **4** in 78% yield.[10]

Then a stereocontrolled methylation reaction was performed to establish the stereochemistry at C11. After treatment of bridged lactone **4** with LDA in THF at −78 °C, a mixture of methyl iodide/HMPA in THF was injected to trap the enolate to give the exo isomer **12** as a single product in 92% yield.[4b−d] The stereochemical outcome of this reaction was confirmed by X-ray crystallographic analysis. Due to the insufficiency of direct transformation of exo isomer **12** to endo isomer **13**,[11] the endo isomer **13** was prepared via a two-step procedure in 75% yield: (i) α-methylenation of **4** with sodium hydride and paraformaldehyde in a sealed tube[12] and (ii) stereoselective hydrogenation of the resulting product with 10% Pd/C in EtOAc. After deprotection with BBr_3 and LAH reduction, the serial products **1a** and **1b** were obtained in high yields (Scheme 4). However, the spectral data of synthetic **1a** or **1b** are not in agreement with those of natural product.[3,13] And the solubility of our synthetic products in $CHCl_3$ was very weak (< 1 mg/mL), while the isolated natural product exhibited good solubility in $CHCl_3$ (3 mg/mL in $CHCl_3$). Hence what we have accomplished are the syntheses of the proposed structure **1**.

Subsequently, another two diastereomers **19** and **20** were furnished by using compound **10** as starting material through the same route (Scheme 5). Thus, four diastereomers, bearing four different combinations of stereochemistry at C7, C10, and C11, were achieved from the same starting material and similar route.

Conclusion

In summary, we have achieved the syntheses of four diastereomers of 3,9,12-trihydroxycalamenene in 28−45% yields over 7−10 steps. The stereochemical controls are accomplished by an unusual framework of benzobicyclo-[3.3.1] lactones, which are prepared via an intramolecular Friedel−Crafts-type Michael addition of α,β-unsaturated lactones. This strategy reveals a potentially flexible and stereoselective installation of the three stereocenters embedded in the aromatic diterpenes with a serrulatane or amphilectane skeleton. Further improvements and applications are underway and will be reported in due time.

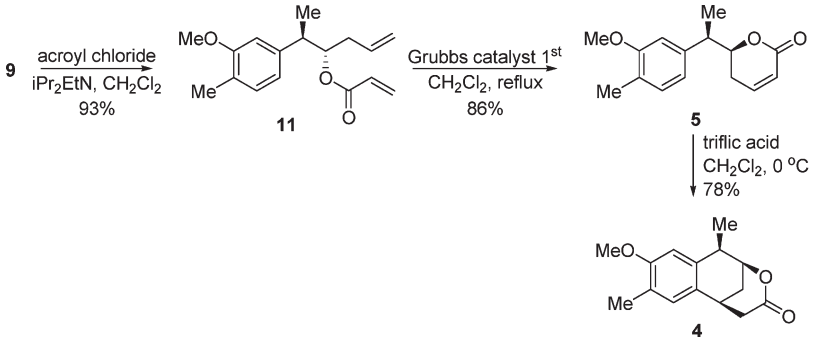
Experimental Section

Typical Procedure for Intramolecular Friedel−Crafts-Type Michael Addition (Compound 8a). To a solution of compound **7a** (118 mg, 0.5 mmol) in 5 mL of CH_2Cl_2 was added triflic acid (0.11 mL, 1.25 mmol, 2.5 equiv) at room temperature, and the mixture was stirred at this temperature open to the air for 24 h. A solution of saturated $NaHCO_3$ was added to the above mixture and the mixture was extracted with CH_2Cl_2, then the combined organic fractions were washed with brine followed by drying over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided 85 mg of compound **8a** in 72% yield as a white solid: mp 109−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 8.4, 2.4 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H), 5.11 (d, J = 1.2 Hz, 1H), 3.78 (s, 3H), 3.21−3.25 (m, 2H), 3.08 (dd, J = 17.6, 4.0 Hz, 1H), 2.80 (dd, J = 18.0, 5.6 Hz, 1H), 2.61 (dt, J = 17.6, 2.0 Hz, 1H), 2.30 (dt, J = 13.6, 2.4 Hz, 1H), 2.11 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 158.9, 132.0, 130.4, 129.6, 114.1, 113.6, 74.5, 55.3, 40.2, 36.5, 30.4, 28.1; HRMS (ESI) calcd for $C_{13}H_{18}NO_3$ $[M + NH_4]^+$ 236.1287, found 236.1282.

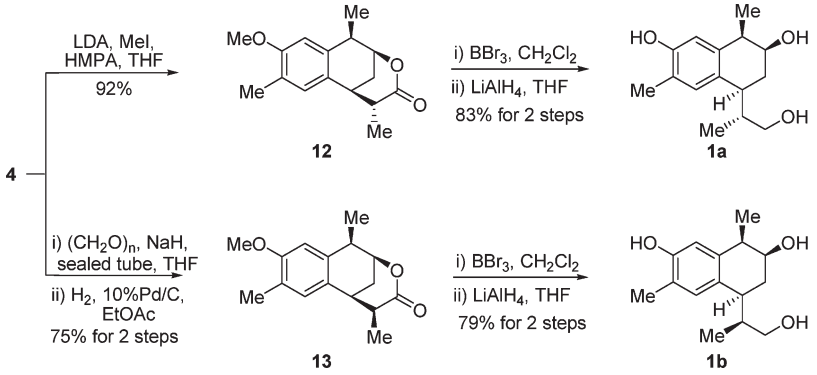
***anti*-2-(3-Methoxy-4-methylphenyl)hex-5-en-3-ol (9).** To a solution of aldehyde **6** (356 mg, 2 mmol) in 2 mL of saturated aqueous ammonium chloride and 0.4 mL of THF were added allyl bromide

(6) Reetz, M. T.; Haning, H. *J. Organomet. Chem.* **1997**, *541*, 117.
(7) Wilson, S. R.; Guazzaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087.
(8) Yamamoto, Y.; Matsuoka, K.; Nemoto., H. *J. Am. Chem. Soc.* **1988**, *110*, 4475.
(9) D'Annibale, A.; Ciaralli, L.; Bassetti, M.; Pasquini, C. *J. Org. Chem.* **2007**, *72*, 6067.
(10) The reaction of **5** at room temperature resulted to the decomposition of starting material. The reason might be the presence of the benzyl methyl group.
(11) The ^{1}H NMR data showed that about 70% conversion was obtained after the treatment of **12** with LDA; however, the two diastereomers were unseparable.
(12) (a) Merten, J.; Hennig, A.; Schwab, P.; Fröhlich, R.; Tokalov, S. V.; Gutzeit, H. O.; Metz, P. *Eur. J. Org. Chem.* **2006**, 1144. (b) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960.
(13) Comparisons of the spectral data of compounds **1a** and **1b** with those of the isolated compound **1** are listed in the Supporting Information.

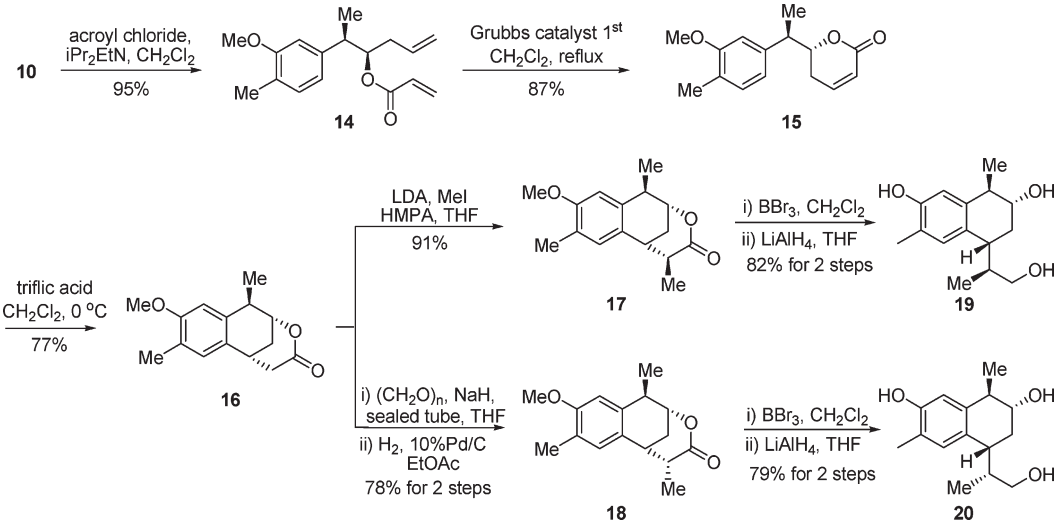
SCHEME 3. Synthesis of Bridged Lactone 4



SCHEME 4. Completion of Syntheses of 3,9,12-Trihydroxycalamenene Diastereomers 1a and 1b



SCHEME 5. Syntheses of Another Two 3,9,12-Trihydroxycalamenene Diastereomers 19 and 20



(484 mg, 0.346 mL, 4 mmol) and zinc dust (256 mg, 4 mmol). The mixture was stirred at room temperature open to the air for 1 h, the suspension was then extracted with Et_2O, and the ether layer was dried over Na_2SO_4. Evaporation of the organic solvent at reduced pressure and purification by flash chromatography yielded 422 mg (96%) of the products in a ratio of 1:2 of antiproduct **9**:syn-product **10**.

To a mixture of PCC (1.24 g, 5.76 mmol) and silica gel (1.24 g) in 20 mL of CH_2Cl_2 was added the resulting products (422 mg, 1.92 mmol) in the above procedure at 0 °C. After being stirred overnight, the mixture was filtered directly by silica gel and then purification by flash chromatography provided 377 mg of ketone in 90% yield.

A solution of ketone (377 mg, 1.73 mmol) in 20 mL of THF was treated with 1 M L-Selectride (2.59 mL, 2.59 mmol) at −78 °C under argon atmosphere. After being stirred at the same temperature for 2 h, the mixture was treated with 3 M NaOH and 30% H_2O_2. The reaction mixture was warmed to room temperature and stirred for 12 h before being extracted with Et_2O. The organic layer was washed with brine then dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided 288 mg of the antiproduct **9** exclusively in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 7.6 Hz, 1H), 6.77 (dd, J = 7.6, 1.2 Hz, 1H), 6.74 (s, 1H), 5.88−5.99 (m, 1H), 5.17 (dd, J = 17.6, 1.2 Hz, 1H), 5.16 (d, J = 10.0 Hz, 1H),

3.86 (s, 3H), 3.72−3.77 (m, 1H), 2.70−2.82 (m, 1H), 2.41−2.47 (m, 1H), 2.22 (s, 3H), 2.13−2.21 (m, 1H), 1.63 (d, J = 3.6 Hz, 1H), 1.31 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 142.1, 135.1, 130.6, 124.8, 119.5, 117.5, 109.9, 75.0, 55.2, 45.4, 38.9, 17.9, 15.8; HRMS (ESI) calcd for $C_{14}H_{24}NO_2$ $[M + NH_4]^+$ 238.1807, found 238.1805.

***syn*-2-(3-Methoxy-4-methylphenyl)hex-5-en-3-ol (10).** To a stirred suspension of indium powder (230 mg, 2 mmol) in 2 mL of THF was added allyl bromide (362 mg, 0.26 mL, 3 mmol) under argon atmosphere, and the indium metal is consumed within 0.5 h in an exothermic reaction, affording a slightly cloudy solution of allyl sesquibromide. At −78 °C, a solution of lithium neopentoxide, which is prepared by adding 4 mmol of BuLi to 4 mmol of neopentyl alcohol in 5 mL of THF at 0 °C for 20 min, was added to the above prepared reagent. After the resulting mixture was stirred for 30 min at −78 °C, a solution of compound **6** (356 mg, 2 mmol) in 1 mL of THF was added. After 2 h at −78 °C, the temperature is gradually allowed to reach room temperature, and the reaction was terminated by treatment with saturated aqueous NH_4Cl solution. It was extracted with Et_2O and the combined organic fractions were washed with brine and then dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided 418 mg (95%) of the products in a ratio of 1:8.5 of antiproduct **9**: syn-product **10**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 6.69 (s, 1H), 5.78−5.89 (m, 1H), 5.14 (d, J = 10.8 Hz, 1H), 5.13 (d, J = 16.4 Hz, 1H), 3.85 (s, 3H), 3.71−3.74 (m, 1H), 2.73−2.80 (m, 1H), 2.23−2.27 (m, 1H), 2.21 (s, 3H), 2.04−2.11 (m, 1H), 1.72 (d, J = 2.8 Hz, 1H), 1.36 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 143.3, 135.2, 130.5, 124.6, 119.3, 118.0, 109.6, 75.0, 55.2, 45.3, 39.5, 16.3, 15.8; HRMS (ESI) calcd for $C_{14}H_{24}NO_2$ $[M + NH_4]^+$ 238.1807, found 238.1806.

***anti*-2-(3-Methoxy-4-methylphenyl)hex-5-en-3-yl Acrylate (11).** To a stirred solution of compound **9** (220 mg, 1 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added diisopropylethylamine (516 mg, 0.69 mL, 4 mmol) and acryloyl chloride (181 mg, 0.162 mL, 2 mmol), and the mixture was stirred for 2 h. Water was added and the mixture was extracted with CH_2Cl_2, then the combined organic fractions were washed with brine followed by drying over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided 255 mg of the ester **11** in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 7.6 Hz, 1H), 6.74−6.77 (m, 2H), 6.35 (dd, J = 17.2, 1.2 Hz, 1H), 6.07 (dd, J = 17.2, 10.4 Hz, 1H), 5.71−5.81 (m, 2H), 5.23 (dt, J = 7.2, 5.6 Hz, 1H), 5.06 (dd, J = 15.6, 1.2 Hz, 1H), 5.05 (d, J = 11.6 Hz, 1H), 3.83 (s, 3H), 3.01−3.08 (m, 1H), 2.26−2.36 (m, 2H), 2.20 (s, 3H), 1.31 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 157.4, 141.3, 133.8, 130.3, 130.2, 128.7, 124.7, 119.9, 117.7, 110.1, 76.8, 55.2, 42.7, 36.1, 17.4, 15.8; HRMS (ESI) calcd for $C_{17}H_{26}NO_3$ $[M + NH_4]^+$ 292.1913, found 292.1912.

***anti*-5,6-Dihydro-6-(1-(3-methoxy-4-methylphenyl)ethyl)pyran-2-one (5).** To a solution of Grubbs catalyst first (82 mg, 0.10 mmol) in 200 mL of CH_2Cl_2 was added a solution of the ring-closing metathesis precursor **11** (548 mg, 2 mmol) in 2 mL of CH_2Cl_2 under argon atmosphere. The mixture was warmed to reflux and stirred for 12 h. After evaporation of the organic solvent at reduced pressure and purification by flash chromatography, 423 mg of the product **5** was obtained in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.6 Hz, 1H), 6.81−6.85 (m, 1H), 6.74−6.76 (m, 2H), 5.97 (dd, J = 9.6, 2.0 Hz, 1H), 4.59 (dt, J = 12.4, 4.4 Hz, 1H), 3.83 (s, 3H), 3.06−3.13 (m, 1H), 2.25−2.34 (m, 1H), 2.21 (s, 3H), 2.14−2.19 (m, 1H), 1.44 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 157.7, 145.4, 140.0, 130.4, 125.2, 121.1, 120.0, 110.2, 81.5, 55.3, 43.3, 26.4, 16.2, 15.8; HRMS (ESI) calcd for $C_{15}H_{22}NO_3$ $[M + NH_4]^+$ 264.1600, found 264.1594.

***rel*-(±)-(7*S*,9*S*,10*R*)-4,10-Dimethyl-3-methoxybenzobicyclo[3.3.1]lactone (4).**[14] Following the procedure described above for the preparation of compound **8a** at 0 °C, 191 mg of compound **4** was obtained in 78% yield as a white solid: mp 130−132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.68 (s, 1H), 4.83−4.86 (m, 1H), 3.81 (s, 3H), 3.18 (s, 1H), 3.05−3.11 (m, 1H), 2.80 (dd, J = 17.6, 5.6 Hz, 1H), 2.62 (dt, J = 17.6, 2.0 Hz, 1H), 2.31 (ddd, J = 13.6, 5.2, 2.4 Hz, 1H), 2.17 (s, 3H), 2.10−2.16 (m, 1H), 1.50 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 157.4, 134.5, 130.4, 129.5, 125.8, 108.8, 79.1, 55.4, 40.7, 38.9, 31.1, 29.0, 17.2, 15.7; HRMS (ESI) calcd for $C_{15}H_{22}NO_3$ $[M + NH_4]^+$ 264.1600, found 264.1598.

***rel*-(±)-(7*S*,9*S*,10*R*,11*R*)-3-Methoxy-4,10,11-trimethylbenzobicyclo[3.3.1]lactone (12).** To a stirred solution of lithium diisopropylamide, prepared from diisopropylamine (71 mg, 0.10 mL, 0.7 mmol) and *n*-butyllithium (1.79 M in hexane, 0.34 mL, 0.6 mmol) in THF, was added compound **4** (123 mg, 0.5 mmol) in 1 mL of THF under argon at −78 °C. After being stirred at the same temperature for 1 h, a solution of methyl iodide (284 mg, 0.23 mL, 2 mmol) and HMPA (89 mg, 0.5 mmol) in 0.5 mL of THF was added and the temperature was allowed to rise to −30 °C. After being stirred at the same temperature for 2 h, the reaction mixture was quenched by addition of saturated NH_4Cl solution. It was then extracted with Et_2O and the combined organic fractions were washed with brine then dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided 120 mg of the product **12** in 92% yield as a white solid: mp 144−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.68 (s, 1H), 4.80−4.82 (m, 1H), 3.81 (s, 3H), 3.06−3.10 (m, 1H), 2.85 (d, J = 1.6 Hz, 1H), 2.71 (ddt, J = 14.8, 7.6, 1.2 Hz, 1H), 2.49 (ddd, J = 13.6, 5.2, 2.4 Hz, 1H), 2.18 (s, 3H), 1.99 (ddd, J = 13.6, 3.2, 1.2 Hz, 1H), 1.50 (d, J = 7.6 Hz, 3H), 1.46 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 157.3, 134.4, 130.5, 125.9, 108.7, 79.1, 55.4, 44.9, 38.8, 37.7, 24.3, 19.0, 17.2, 15.7 (1 C not observed due to overlap); HRMS (ESI) calcd for $C_{16}H_{24}NO_3$ $[M + NH_4]^+$ 278.1756, found 278.1757.

***rel*-(±)-(7*S*,9*S*,10*R*,11*S*)-3-Methoxy-4,10,11-trimethylbenzobicyclo[3.3.1]lactone (13).** To a solution of the lactone **4** (49 mg, 0.2 mmol) in THF (5 mL) in a sealed tube was added paraformaldehyde (180 mg, 6 mmol) and NaH (29 mg, 1.2 mmol). The colorless mixture was stirred at 100 °C for ca. 40 min. A change in the color of the mixture to yellowish brown within this time period indicates termination of the reaction, and the heating source was removed immediately. The resulting solution was cooled to room temperature and quenched by water. Then it was extracted with Et_2O and the combined organic fractions were washed with brine then dried over Na_2SO_4, filtered, and concentrated. Purification was by flash chromatography and the crude product was dissolved in EtOAc. After adding 10% Pd/C, the resulting suspension was stirred under H_2 atmosphere for 4 h at room temperature. Then it was filtered and concentrated and purified by flash chromatography to provide 39 mg of the product **13** in 75% yield for 2 steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.71 (s, 1H), 4.81−4.83 (m, 1H), 3.81 (s, 3H), 3.04−3.08 (m, 1H), 2.99 (s, 1H), 2.75−2.83 (m, 1H), 2.46 (ddd, J = 13.5, 4.8, 1.8 Hz, 1H), 2.23 (d, J = 4.2 Hz, 1H), 2.18 (s, 3H), 1.49 (d, J = 7.2 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 157.4, 135.0, 132.5, 125.9, 124.4, 108.8, 79.1, 55.3, 42.8, 39.4, 36.8, 31.3, 17.3, 15.8, 15.1; HRMS (ESI) calcd for $C_{16}H_{24}NO_3$ $[M + NH_4]^+$ 278.1756, found 278.1758.

***rel*-(±)-(7*S*,9*S*,10*R*,11*R*)-3,9,12-Trihydroxycalamenene (1a).** To a solution of compound **12** (20 mg, 0.077 mmol) in 3 mL of CH_2Cl_2 was added BBr_3 (1 M in CH_2Cl_2, 0.23 mL, 0.23 mmol) solution under argon atmosphere at −78 °C, and the resulting solution was allowed to rise to −20 °C. After being stirred at the same temperature for 12 h, the reaction mixture

(14) Note that it was just relative configuration.

was quenched by water. Then it was extracted with CH_2Cl_2 and the combined organic fractions were washed with brine then dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided the crude product.

To a suspension of $LiAlH_4$ (8.7 mg, 0.23 mmol) in 2 mL of THF was added the resulting crude product at 0 °C, and the mixture was allowed to rise to room temperature. After being stirred for 3 h at room temperature, the mixture was quenched by water. It was extracted with EtOAc and the combined organic fractions were washed with brine then dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided 16 mg of the product **1a** in 83% yield for 2 steps. ^{1}H NMR (300 MHz, acetone-d_6) δ 7.83 (s, 1H), 7.03 (s, 1H), 6.52 (s, 1H), 3.84−3.91 (m, 1H), 3.71 (d, J = 4.2 Hz, 1H), 3.34−3.40 (m, 1H), 3.25−3.32 (m, 2H), 2.88−2.94 (m, 1H), 2.78−2.85 (m, 1H), 2.35−2.40 (m, 1H), 2.14 (s, 3H), 1.76−1.83 (m, 1H), 1.50−1.63 (m, 1H), 1.12 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 154.2, 142.1, 129.9, 129.0, 123.1, 115.8, 69.9, 64.2, 41.5, 40.9, 40.4, 28.1, 16.8, 16.2 (1 C not observed due to overlap); IR (KBr) 3343, 1694, 1619, 1458, 1416, 1256, 1029 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{22}NaO_3$ [M + Na]$^+$ 273.1467, found 273.1460.

***rel*-(±)-(7*S*,9*S*,10*R*,11*S*)-3,9,12-Trihydroxycalamenene (1b).** Following the procedure described above for the preparation of compound **1a**, 14 mg of product **1b** was obtained in 79% yield for 2 steps. ^{1}H NMR (300 MHz, acetone-d_6) δ 7.80 (s, 1H), 6.97 (s, 1H), 6.52 (s, 1H), 3.89−3.95 (m, 1H), 3.71 (d, J = 4.2 Hz, 1H), 3.64 (t, J = 5.1 Hz, 1H), 3.52−3.57 (m, 2H), 3.20 (ddd, J = 11.1, 7.5, 3.6 Hz, 1H), 2.79−2.86 (m, 1H), 2.42−2.47 (m, 1H), 2.14 (s, 3H), 1.54−1.67 (m, 2H), 1.12 (d, J = 7.2 Hz, 3H), 0.61 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 154.0, 142.5, 129.5, 129.2, 123.2, 115.8, 69.6, 66.2, 40.8, 39.9, 38.0, 25.9, 17.0, 16.2, 11.2; IR (KBr) 3341, 1695, 1619, 1462, 1415, 1256, 1030 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{22}NaO_3$ [M + Na]$^+$ 273.1467, found 273.1461.

***rel*-(±)-(7*R*,9*R*,10*R*,11*S*)-3,9,12-Trihydroxycalamenene (19).** Following the procedure described above for the preparation of compound **1a**, product **19** was obtained in 82% yield for 2 steps. ^{1}H NMR (300 MHz, acetone-d_6) δ 7.81 (d, J = 3.0 Hz, 1H), 7.01 (s, 1H), 6.74 (s, 1H), 3.86 (t, J = 4.5 Hz, 1H), 3.35−3.43 (m, 2H), 3.22−3.35 (m, 2H), 2.80−2.93 (m, 1H), 2.46−2.56 (m, 1H), 2.28−2.35 (m, 1H), 2.15 (s, 3H), 2.07−2.12 (m, 1H), 1.37−1.48 (m, 1H), 1.30 (d, J = 6.9 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 154.3, 140.5, 130.0, 129.8, 122.3, 113.7, 74.0, 64.3, 42.5, 41.4, 40.3, 34.7, 17.6, 16.2, 16.1; IR (KBr) 3353, 1695, 1617, 1451, 1415, 1257, 1030 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{22}NaO_3$ [M + Na]$^+$ 273.1467, found 273.1458.

***rel*-(±)-(7*R*,9*R*,10*R*,11*R*)-3,9,12-Trihydroxycalamenene (20).** Following the procedure described above for the preparation of compound **1a**, product **20** was obtained in 79% yield for 2 steps. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.83 (d, J = 2.0 Hz, 1H), 6.95 (s, 1H), 6.76 (s, 1H), 3.87 (t, J = 5.2 Hz, 1H), 3.72 (s, 1H), 3.49−3.58 (m, 2H), 3.31−3.38 (m, 1H), 3.18−3.23 (m, 1H), 2.45−2.55 (m, 1H), 2.40−2.44 (m, 1H), 2.15 (s, 3H), 1.94−2.00 (m, 1H), 1.42 (q, J = 7.6 Hz, 1H), 1.32 (d, J = 6.8 Hz, 3H), 0.59 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 154.2, 140.9, 130.2, 129.2, 122.5, 113.7, 73.8, 66.2, 42.5, 39.8, 38.0, 32.8, 17.5, 16.1, 11.2; IR (KBr) 3352, 1695, 1619, 1505, 1462, 1415, 1256, 1038 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{22}NaO_3$ [M + Na]$^+$ 273.1467, found 273.1463.

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Supporting Information Available: Experimental procedures and spectral data for all new products, X-ray crystallographic data (CIF), and ORTEP diagrams for compounds **12**. This material is available free of charge via the Internet at http://pubs.acs.org.