Reactive Enols in Synthesis 2. Synthesis of (+)-Latifolic Acid and (+)-Latifoline

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We describe a short, enantioselective synthesis of the naturally occurring pyrrolizidine alkaloid (+)-latifoline (**1**) employing a tandem [3,3] sigmatropic rearrangement/[1,2] allyl shift as a key step in constructing (+)-latifolic acid (**4**).

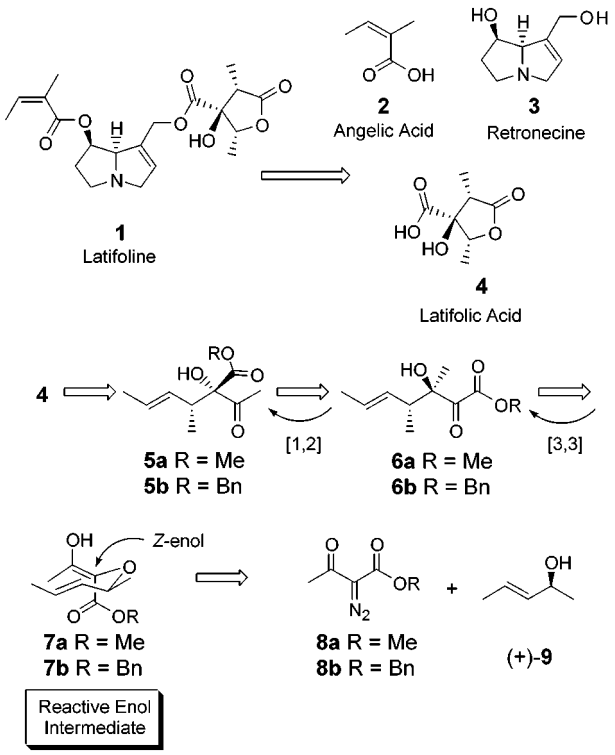
Introduction

Bifunctional pyrrolizidine alkaloids (e.g., latifoline, heliosupine, indicine *N*-oxide, monocrotaline, senecionine, etc.) are well-known to exhibit interesting biological properties, including activity against various forms of leukemia and solid tumors.[1] In general, this anti-cancer activity is attributed to the alkaloid's capacity to block DNA replication by either DNA−protein or DNA−interstrand cross-linking; however, the structural subtleties that dictate the mode of action remain enigmatic. Latifoline (**1**), a member of the pyrrolizidine class, was first isolated in 1962 by Crowley and Culvenor[2] from *Cynoglossum latifolium*, an Australian representative of the Boraginaceae family.

To date, despite extensive synthetic efforts toward a number of pyrrolizidine alkaloids,[3] a synthesis of latifoline has yet to be reported. Herein, we describe an efficient asymmetric synthesis of latifolic acid and its use in assembling (+)-latifoline.

From a retrosynthetic perspective (Scheme 1), the availability of angelic acid (**2**) and retronecine (**3**) from commercial sources left assembly of latifolic acid (**4**)[4] as the primary synthetic challenge in preparing compound **1**. To this end, we recognized that **4** could readily arise from open-chain intermediate **5**, which in turn could be accessed via a tandem [3,3]/[1,2] rearrangement of the reactive enol (**7**) produced upon Rh(II)-initiated coupling of **8** and **9**.[5]

Scheme 1. Latifoline: Retrosynthetic Analysis



Results and Discussion

To test the viability of the proposed route, we sought to prepare the known methyl ester **13a**[4] (Scheme 2). Toward this end, **8a**[6] and (±)-(**9**) were subjected to a rhodium-initiated [3,3] rearrangement that efficiently delivered α-hydroxy ketone (±)-**6a** as a 6:1 diastereomeric mixture. Mechanistically, the reaction proceeds initially to a *Z*-enol intermediate that then undergoes [3,3] rearrangement through a chairlike transition state (see (±)-**7a** in Scheme 1). This scenario, coupled with the *E*-geometry of the allylic alcohol, accounts for the relative configuration of the major product (±)-**6a**, whereas a boatlike transition state is responsible for the formation of the minor diastereomer.[7]

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(1) Rajski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723−2795.

(2) Crowley, H. C.; Culvenor, C. C. J. *Aust. J. Chem.* **1962**, *15*, 139−144.

(3) (a) Liu, Z. Y.; Zhao, L. Y. *Tetrahedron Lett.* **1999**, *40*, 5593−5596. (b) Niwa, H.; Ogawa, T.; Okamoto, O.; Yamada, K. *Tetrahedron* **1992**, *48*, 10531−48. (c) Niwa, H.; Miyachi, Y.; Okamoto, O.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. *Tetrahedron* **1992**, *48*, 393−412. (d) Nishimura, Y.; Kondo, S.; Umezawa, H. *Tetrahedron Lett.* **1986**, *27*, 4323−6. (e) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954−61.

(4) In an effort to determine the relative stereochemistry of latifolic acid, Matsumoto accomplished a stereorandom synthesis of all four possible diastereomers. (a) Matsumoto, T.; Okabe, T.; Fukui, K. *Chem. Lett.* **1972**, 29−32. (b) Matsumoto, T.; Okabe, T.; Fukui, K. *Chem. Lett.* **1973**, 773−776.

(5) For other uses of reactive enols in synthesis, see: Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.* **1999**, *121*, 6326−6327.

(6) Prepared from the corresponding β-oxobutanoate ester. For a general procedure, see: Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709−1716.

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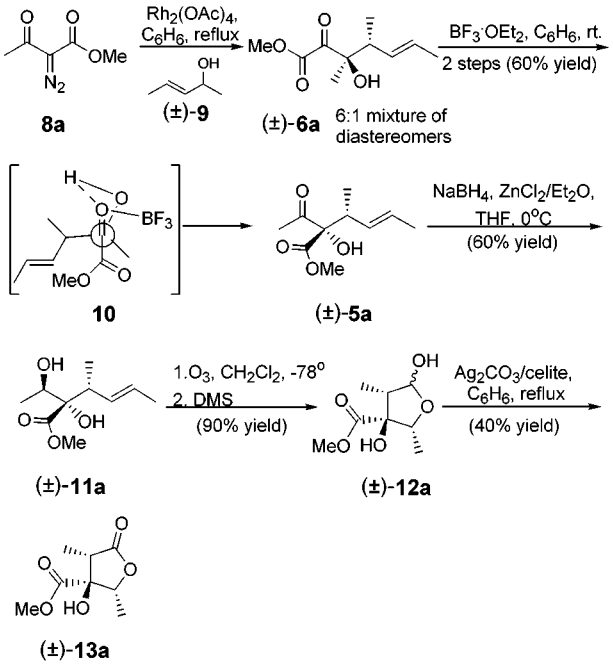
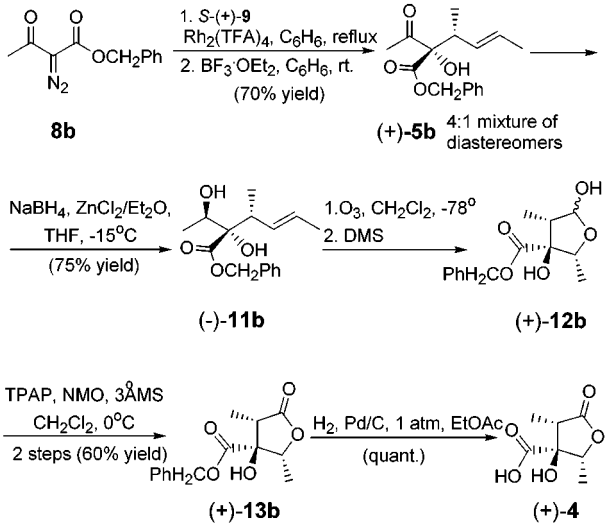
Scheme 2. Synthesis of (±)-Latifolic Acid Methyl Ester



Exposure of crude (±)-**6a** to $BF_3{\cdot}OEt_2$ effected a completely diastereoselective 1,2-allyl shift[8] to yield (±)-**5a**[9] (same 6:1 ratio). The stereochemical outcome of the reaction is consistent with a syn-periplanar transition state **10**. Unfavorable steric interactions disrupting this conformation could lead to lower stereoselectivity, as observed when the methyl ester is replaced with a benzyl ester (vide infra). Subsequent reduction of (±)-**5a** with sodium borohydride/zinc chloride followed by reductive ozonolysis furnished lactols (±)-**12a**.[10] Finally, oxidation of **12a** with Celite-supported silver carbonate[11] produced the corresponding lactone (±)-**13a**, which was found to be spectroscopically in accord with literature values.[4] Unfortunately, attempts to advance **13a** to **4** via hydrolysis of the methyl ester led to complex mixtures.

Having secured the route in terms of relative stereochemistry we focused our efforts on completing an enantioselective synthesis of **4**. To this end, sequential treatment of benzyl diazoacetoacetate (**8b**)[6] and (*S*)-(+)-(**9**) (98% ee)[7a] with $Rh_2(TFA)_4$ and $BF_3{\cdot}OEt_2$ afforded a 4:1 mixture of diastereomeric alcohols **5b** in 70% yield (94% ee)[12] (Scheme 3). Subsequent chelation-controlled

Scheme 3. Synthesis of (+)-Latifolic Acid



reduction and reductive ozonolysis of (+)-**5b** proceeded smoothly to furnish (+)-**12b** which, upon exposure to TPAP,[13] gave lactone (+)-**13b**.[14] To our delight, deprotection of the benzyl ester under hydrogenolytic conditions produced (+)-latifolic acid (**4**) in quantitative yield. The spectroscopic and physical properties of the product were identical to those reported for natural (+)-latifolic acid.[4,15]

With ample quantities of optically active latifolic acid in hand, we began exploring the double esterification of (+)-retronecine (**3**),[16] a task that proved to be nontrivial (Scheme 4). Thus, after considerable experimentation, it was found that protection of the C9-OH as the corresponding TBS-ether (+)-**14** followed by sequential treatment of the remaining alcohol with *n*-BuLi and excess angelyl chloride affords angelate (+)-**15**.

In our efforts to convert (+)-**15** to (+)-**16**, isomerization of the angelate moiety to the thermodynamically preferred tiglate proved problematic even under nonbasic conditions (use of CAN/MeOH led to a 1:1 mixture of diastereomers). We eventually discovered that when SiF_4[17] was used as a mild source of fluoride we were able to isolate (+)-**16** in excellent yield without any tiglate contamination. Poised for the final acylation, difficulties associated with the lability of (+)-**4** toward base and the sterically congested carboxylic acid moiety proved to be the next obstacles. We sought to circumvent the steric hindrance at the sp^2 reaction center by converting the primary allylic alcohol into a good leaving group (-Br, -Cl, -OMs, Mitsunobu conditions) and using the carboxylate unit as a nucleophile. Unfortunately, none of these conditions produced the desired ester. Use of a number of commonly employed activating agents (DCC, DMAP, HOBt, PyBop, etc.) led to no reaction, whereas use of base to activate the primary allylic alcohol promoted decomposition of latifolic acid. Eventually, it was determined

(7) For a detailed discussion concerning the mechanism and stereoselectivity of the Rh-initiated Claisen rearrangement, see: (a) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H−J. *J. Am. Chem. Soc.* **1999**, *121*, 1748−1749. (b) Wood, J. L.; Moniz, G. A. *Org. Lett* **1999**, *1*, 371−374 and references therein.

(8) Wood, J. L.; Stoltz, B. M.; Dietrich, H−J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641−9651.

(9) Compound (±)-**5a** has recently been employed by our research group in the synthesis of (±)-K252A analogues. See: Tamaki, K.; Shotwell, J. B.; White, R. D.; Drutu, I.; Petsch, D.; Nheu, T. V.; He, H.; Hirokawa, Y.; Maruta, H.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1689.

(10) The series of reactions leading to (±)-**11a** was performed on the 6:1 diastereomeric mixture obtained upon rearrangement of (±)-**7a**. The minor diastereomer was omitted from the schemes for clarity; the yields of (±)-**5a** and (±)-**11a** refer to the mixture, all the other yields reflect the amount of desired diastereomer. The chelation controlled reduction also furnished a 6:1 mixture of diastereomeric diols (±)-**11a**, indicating complete stereoselectivity.

(11) McKillop, A.; Young, D. W. *Synthesis* **1979**, 401−422.

(12) The major diastereomer (shown in Scheme 3) can be isolated by HPLC. The minor diastereomer has the opposite absolute configuration at the tertiary hydroxyl (for discussion see ref 7).

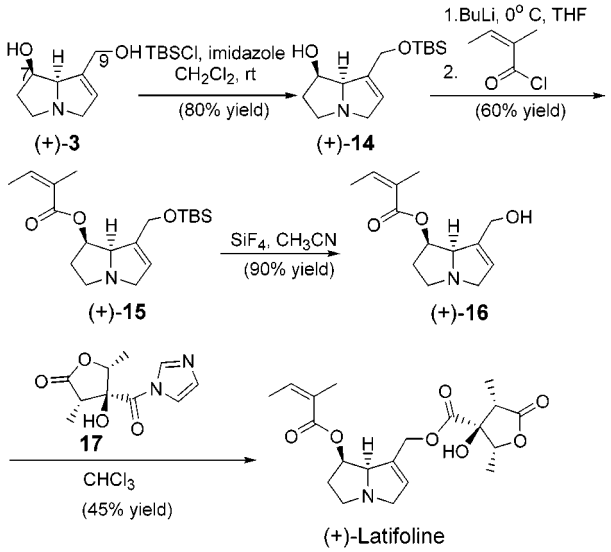
(13) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *7*, 639−666.

(14) For practical purposes, the reactions leading to **13b** were typically performed on the 4:1 diastereomeric mixture. The yield of **11b** refers to the 4:1 mixture, whereas the yield of **13b** reflects the amount of diastereomerically pure lactone obtained by crystallization of the crude reaction product.

(15) Roitman, J. N. *Aust. J. Chem.* **1988**, *41*, 1827−1833.

(16) Sufficient amounts of retronecine (**3**) were obtained via reductive cleavage of monocrotaline. For details see, Supporting Information.

Scheme 4. Completion of (+)-Latifoline



that lengthy exposure of (+)-**16** to the preformed latifolic acid imidazolide (**17**)[18] was a suitable method for effecting the desired coupling and afforded latifoline in reasonable yield (45%) as a white crystalline solid.[19] The synthetic material was identical in all respects to naturally occurring (+)-latifoline.

In summary, we accomplished an efficient, enantioselective synthesis of (+)-latifoline (seven steps for the longest linear sequence, 14% overall yield starting from benzyl diazoacetoacetate, 21% overall yield starting from retronecine).

Experimental Section

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Methylene chloride (CH_2Cl_2), benzene (PhH), and triethylamine (Et_3N) were distilled from calcium hydride. All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 precoated plates (0.25 mm). Flash chromatography was performed with the indicated solvent system using Silicycle 0.040−0.060 mm silica gel. Concentration refers to the removal of solvent with a rotary evaporator at normal aspirator pressure followed by further evacuation with a two-stage mechanical pump. All melting points are uncorrected. Infrared spectra were recorded on Brucker Avance DPX-500 and Brucker Avance DPX-400 spectrometers. High-resolution mass spectra were performed at the University of Illinois Mass Spectroscopy Center. Normal-phase high-performance liquid chromatography (HPLC) was performed on a Waters model 510 system using a Rainin Microsorb 80-199-C5 column. Optical rotations were determined on a Perkin-Elmer model 341 polarimeter.

Preparation of Diol 11a. To 0.37 g (10 mmol) of $NaBH_4$ in a dry round-bottom flask immersed in an ice bath was added a 1 M $ZnCl_2/Et_2O$ solution (10 mL, 10 mmol) followed by a solution of **5a** (2.0 g, 10 mmol) in THF (20 mL). After 20 min, the reaction was quenched by slow addition of water (50 mL). The aqueous layer was extracted with Et_2O (3 × 75 mL). The combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (EtOAc:hexane/20:80) to furnish **11a** (1.2 g, 60% yield, 6:1 diastereomeric mixture) as a yellow oil. An analytically pure sample of the major diastereomer was obtained by HPLC on silica gel, using EtOAc/hexane/17:83: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (d, J = 7 Hz, 3H), 1.20 (d, J = 6 Hz, 3H), 1.67 (d, J = 5 Hz, 3H), 1.95 (br s, 1H), 2.55 (quintet, J = 7 Hz, 1H), 3.35 (s, 1H), 3.84 (s, 3H), 3.95 (m, 1H), 5.44−5.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.25, 17.21, 18.08, 42.34, 52.79, 69.77, 82.68, 126.95, 131.28, 175.73; IR (thin layer, NaCl) 1007 (s), 1083 (s), 1149 (s), 1225 (s), 1730 (s), 2850−3000 (m), 3200−3550 (m) cm^{-1}; HRMS (FAB) m/z 203.1284,calcd for $C_{10}H_{17}O_4$ 203.1283.

Preparation of Lactol 12a. A cooled (−78 °C) solution of **11a** (0.7 g, 3.46 mmol) in CH_2Cl_2 (10 mL) was treated with ozone (9 mL/min) until the solution turned slightly blue (about 5 min). The solution was purged with N_2 until the blue color disappeared, and then dimethyl sulfide (5 mL) was added. The cold bath was removed, and the solution was stirred at room temperature for 1 h. Evaporation of solvent under a nitrogen stream, followed by flash chromatography on silica gel (EtOAc/hexane 20:80), afforded **12a** (0.58 g, 90% yield, 1:1 mixture of diastereomers) as a white solid: mp 90−91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, J = 7 Hz, 3H), 1.08 (d, J = 7 Hz, 3H), 1.16 (d, J = 6 Hz, 3H), 1.21 (d, J = 6 Hz, 3H), 2.45 (quintet, J = 7 Hz, 1H), 2.61 (quintet, J = 7 Hz, 1H), 3.25 (br s, 1H), 3.55 (br s, 1H), 3.90 (s, 3H), 3.93 (s, 3H), 3.98 (q, J = 6 Hz, 1H), 4.32 (q, J = 6 Hz, 1H), 5.24 (d, J = 6 Hz, 1H), 5.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.05, 9.90, 14.27, 15.21, 47.68, 51.38, 52.76, 53.21, 79.03, 81.33, 85.02, 85.47, 98.61, 102.78, 173.06, 173.96; IR (thin film, NaCl plate) 1065 (s), 1142 (s), 1231 (s), 1727 (s), 2800−3000 (m), 3200−3600 (m) cm^{-1}; HRMS (FAB) m/z 213.0740, calcd for $C_8H_{14}O_5Na$ 213.0738 (M^+-Na).

Preparation of Latifolic Acid Methyl Ester (13a). A solution of lactol **12a** (100 mg, 0.52 mmol) in benzene (4 mL) was added to a dry round-bottom flask containing $AgCO_3$/Celite (50wt %, 500 mg, 0.9 mmol). The flask was submerged in a preheated oil bath, and the mixture was brought to reflux for 2 h. An additional portion of $AgCO_3$/Celite (500 mg) was added, and the mixure was refluxed for another 30 min. Upon complete consumption of starting material (TLC), the reaction mixture was filtered through a pad of Celite, the solvent evaporated, and the residue purified by flash chromatography on silica gel (EtOAc/hexane 20:80) to yield **13a** (40 mg, 40% yield) as white needles. The physical and spectroscopic data for this synthetic material were in perfect agreement with data reported for racemic latifolic acid methyl ester.[4]

Preparation of Tertiary Alcohol 5b. To a solution of benzyl 2-azo-3-oxobutanoate (6.10 g, 27.98 mmol) and (*S*)-(*E*)-3-penten-2-ol (2.89 g, 33.57 mmol) in CH_2Cl_2 (150 mL) was added $Rh_2(TFA)_4$ (65 mg, 0.1 mmol). The mixture was immersed in a preheated oil bath, and after 5 h at reflux, the reaction was judged complete by TLC. After the mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the residue dissolved in benzene (150 mL). The resultant solution was cooled to 0 °C and treated with $BF_3{\cdot}OEt_2$ (4.12 mL, 33.57 mmol). After 2 h, the reaction was quenched with saturated $NaHCO_3$ (15 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). After the combined organic extracts were dried over Na_2SO_4, the solvent was evaporated and the residue chromatographed on silica gel using EtOAc/hexane 5:95 as eluent to yield **5b** (5.37 g, 70% yield, 4:1 mixture of diastereomers) as a yellow oil. The major diastereomer was isolated in analytically pure form by HPLC, using EtOAc/hexane 10:90 as eluent: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, J = 7 Hz, 3H), 1.53 (d, J = 7 Hz, 3H), 2.29 (s, 3H), 3.17 (quintet, J = 7 Hz, 1H), 4.08 (s, 1H), 5.16 (d, J = 12 Hz, 1H), 5.20. d (12, 1H), 5.31 (m, 1H), 5.44 (m, 1H), 7.35 (m, 5H); ^{13}C NMR (125 MHz, CDCl3) δ 14.63, 18.01, 25.65, 42.82, 68.20, 87.72, 127.92, 128.61, 128.67, 127.70, 129.83, 134.94, 170.38, 205.28; IR (thin film, NaCl plate) 1147 (s), 1194 (s), 1237 (s), 1264 (s), 1720

(17) Corey, E. J.; Yi, K. Y. *Tetrahedron Lett.* **1992**, *33*, 2289−2290.
(18) Hoskins, W. M.; Crout, D. H. G. *J. Chem. Soc., Perkin Trans. 1* **1977**, 538−544.
(19) Attempts to effect the angelate esterification at the C7-OH with the C9-OH latifolate ester in place failed; the harsh conditions required to activate the unusually hindered secondary hydroxyl group invariably led to decomposition.

(s), 2850−3050 (m), 3400−3450 (m) cm^{-1}; HRMS (FAB) *m/z* 277.1441, calcd for $C_{16}H_{21}O_4$ 277.1439 (M^+H); $[\alpha]^{20}_D = +13.1°$ (*c* 1.6, $CDCl_3$). Enantiomeric excess was determined to be 94% by integration of the NMR signals for the major and minor enantiomers using europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate as a chiral shift reagent.

Preparation of Diol 11b. To a cooled (−30 °C) suspension of $NaBH_4$ (0.8 g, 21.62 mmol) in THF (20 mL) was added a 1 M solution of $ZnCl_2/Et_2O$ (19.45 mL, 19.45 mmol), followed by a solution of **5b** (5.37 g, 19.45 mmol, 4:1 diastereomeric mixture) in THF (100 mL). The mixture was allowed to warm to −15 °C, and stirring was continued for 30 min. After this time, TLC showed complete consumption of starting material and the reaction was quenched by adding 1 N HCl until foaming stopped. The biphasic mixture was extracted with three portions of CH_2Cl_2 (100 mL, 50 mL, 50 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4, and the solvent was removed in vacuo. Purification of the residue by flash chromatography on silica gel, using EtOAc/hexane 10:90 → 80:20, gave **11b** (3.96 g, 75% yield, 4:1 mixture of diastereomers). An analytically pure sample of the major diastereomer was obtained by HPLC on silica gel, using EtOAc/hexane 20:80 as eluent: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (d, J = 7 Hz, 3H), 1.18 (d, J = 6.5 Hz, 3H), 1.59 (d, J = 5 Hz, 3H), 1.95 (d, J = 11 Hz, 1H), 2.57 (quintet, J = 4 Hz, 1H), 3.35 (s, 1H), 3.97 (m, 1H), 5.23 (d, J = 12 Hz, 1H), 5.27 (d, J = 12 Hz, 1H), 5.41 (m, 2H), 7.39 (m, 5H); ^{13}C NMR (125 MHz, CDCl3) δ 15.01, 17.25, 18.06, 42.18, 67.90, 69.76, 82.47, 126.96, 128.65, 128.71, 128.74, 131.16, 135.00, 175.12; IR (thin film, NaCl plate) 1005 (s), 1082 (s), 1147 (s), 1216 (s), 1727 (s), 2900−3000 (m), 3300−3600 (m) cm^{-1}; HRMS (FAB) *m/z* 265.1597, calcd for $C_{16}H_{23}O_4$ 269.1596 (M^+H)]; $[\alpha]^{20}_D = -7°$ (*c* 0.4, $CDCl_3$).

Preparation of (+)-Latifolic Acid Benzyl Ester (13b). A cooled (−78 °C) solution of **11b** (3.0 g, 10.79 mmol, 4:1 mixture of diastereomers) in CH_2Cl_2 (10 mL) was treated with ozone (9 mL/min) until the solution turned slightly blue (about 5 min). The solution was purged with N_2 until the blue color disappeared, and then 5 mL of dimethyl sulfide was added. The cold bath was removed, and the solution was stirred at room temperature for 1 h. The solvent was evaporated under a nitrogen stream and the residue taken in CH_2Cl_2 (10 mL). After being cooled to 0 °C, the solution was treated with 3 Å molecular sieves (2.0 g), *N*-methylmorpholine *N*-oxide (5.0 g, 42.66 mmol), and TPAP (200 mg, 0.56 mmol). The reaction was slightly exothermic and was judged complete by TLC after 30 min. The solvent was evaporated and the crude residue washed with water (3 × 100 mL) to remove the dimethyl sulfone formed in the oxidation. Flash chromatography on silica gel (CH_2Cl_2 as eluent) followed by recrystallization from Et_2O/hexane afforded a single diastereomeric product as long white needles (1.7 g, 60% yield from **11b**): mp 72−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 7 Hz, 3H), 1.23 (d, J = 7 Hz, 3H,), 2.93 (q, J = 7 Hz, 1H), 3.76 (s, 1H), 4.39 (q, J = 7 Hz, 1H), 5.33 (s, 2H), 7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.12, 13.34, 45.50, 68.67, 79.51, 83.16, 128.83, 128.86, 129.10, 133.83, 171.65, 174.44; IR (thin film, NaCl) 1073 (s), 1143 (s), 1216 (s), 1738 (s), 1787 (s), 2900−3050 (w), 3350−3550 (m) cm^{-1}; HRMS (FAB) *m/z* 265.1076, calcd for $C_{14}H_{17}O_5$ 265.1075 (M^+H)]; $[\alpha]^{20}_D = +79°$ (*c* 0.75, $CDCl_3$).

Preparation of (+)-Latifolic Acid (4). To a solution of (+)-latifolic acid benzyl ester (**13b**) (0.8 g, 3.03 mmol) in EtOAc (100 mL) was added Pd/C (5wt %) (40 mg). The mixture was vigorously stirred under an H_2 atmosphere (balloon) for 3 h. Filtration through a pad of Celite (under N_2) and concentration of the filtrate produced analytically pure (+)-latifolic acid (0.5 g, quantitative yield) as a white crystalline solid. The physical and spectroscopic properties were in good agreement with published values for (+)-latifolic acid: ^{1}H NMR (500 MHz, acetone-d_6) δ 1.15 (d, J = 7 Hz, 3H), 1.34 (d, J = 7 Hz, 3H), 2.99 (q, J = 7 Hz, 1H), 4.40 (q, J = 7 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 8.80, 13.97, 46.31, 80.27, 83.92, 172.32, 175.13; IR (thin film, NaCl plate) 1072 (s), 1141 (s), 1201 (s), 1748 (s), 2900−3400 (m) cm^{-1}; HRMS (FAB) *m/z* 175.0606, calcd for $C_7H_{11}O_5$ 175.0606 (M^+H); $[\alpha]^{20}_D = +84.4°$ (*c* 2.7, acetone).

Preparation of (+)-14. To a suspension of (+)-retronecine (0.5 g, 3.22 mmol) in CH_2Cl_2 (20 mL) was added TBSCl (0.8 g, 5 mmol), followed by imidazole (0.4 g, 5.8 mmol). The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated $NaHCO_3$ (25 mL). The biphasic mixture was extracted with Et_2O (4 × 100 mL), and the combined organic extracts were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (EtOAc/MeOH 95:5 → 70:30) to yield **14** (695 mg, 80% yield) as a white crystalline solid. The physical and spectral properties of the material matched literature data for (+)-9-TBS retronecine.[3e]

Preparation of 15. To prepare angelyl chloride, a suspension of potassium angelate (725 mg, 5.25 mmol) in ether (20 mL) was treated with a drop of DMF and oxalyl chloride (0.5 mL, 5.25 mmol). The mixture was stirred vigorously at room temperature until the evolution of gas ceased (about 5 h). The mixture was filtered and kept under nitrogen. In a separate flask, a solution of (+)-**14** (500 mg, 1.85 mmol) in THF (20 mL) was cooled to 0 °C. To the cooled solution was added dropwise 1.7 M *n*-BuLi in hexane (1.2 mL, 2.00 mmol). After the solution was stirred for 10 min, the solution of angelyl chloride was added very slowly until thin-layer chromatography showed no further advancement of the reaction (8 mL, ca. 2.1 mmol). The resultant solution was treated again with *n*-BuLi (0.2 mL, 0.34 mmol), followed by 3 mL of the angeloyl chloride solution (ca 0.8 mmol). This process was repeated three times, until TLC showed complete consumption of starting material. The reaction was then adsorbed onto 2 g of silica gel and purified by flash chromatography, using a gradient eluent (EtOAc/MeOH 97.5:2.5 → 90:10) to furnish (+)-**15** (390 mg, 60% yield) as a light brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (d, J = 4 Hz, 6H), 0.885 (s, 9H), 1.81 (quintet, J = 1.5 Hz, 3H), 1.95 (dd, J = 7, 1.5 Hz, 3H), 2.1 (m, 2H), 2.65 (m, 1H), 3.35 (m, 2H), 3.95 (d, J = 14 Hz, 1H), 4.13 (d, J = 14 Hz, 1H), 4.17 (d, J = 14 Hz, 1H), 4.31 (br s, 1H), 5.38 (br s, 1H), 5.64 (br s, 1H), 6.07 (q, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.46, 15.82, 18.35, 20.62, 25.91, 34.79, 53.96, 60.53, 62.86, 73.57, 75.66, 122.98, 127.80, 138.74, 138.91, 166.94; IR (thin film, NaCl plate) 838 (s), 1083 (s), 1159 (s), 1231 (s), 1715 (s), 2855 (s), 2928 (s), 2953 (s) cm^{-1}; HRMS (FAB) *m/z* 352.2307, calcd for $C_{19}H_{34}NO_3Si$ 352.2308 (M^+H); $[\alpha]^{20}_D = +17.5°$ (*c* 3.0, $CDCl_3$).

Preparation of (+)-16. A solution of (+)-**15** (150 mg, 0.43 mmol) in anhydrous CH_3CN (20 mL) was prepared in a dry round-bottom flask. A balloon filled with SiF_4 was attached, and the solution was stirred until complete consumption of starting material was observed by TLC (45 min). The SiF_4 balloon was removed, and N_2 was bubbled through the solution for 5 min. The reaction was quenched by adding water (0.5 mL), and the solvent was evaporated in vacuo. The product was purified by flash chromatography on silica gel, using a gradient eluent (EtOAc → EtOAc/MeOH → MeOH) to yield **16** (90 mg, 90% yield) as a pale tan crystalline solid. The spectroscopic and physical properties match the published data for naturally occurring (+)-7-angelylretronecine: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75 (quintet, J = 1.5 Hz, 3H), 1.90 (dd, J = 13, 3.2, 5 Hz, 3H), 2.05 (m, 2H), 2.61 (q, J = 9 Hz, 1H), 3.2−3.3 (m, 2H), 3.83 (d, J = 14 Hz, 1H), 4.00 (d, J = 13 Hz, 1H), 4.13 (d, J = 14 Hz, 1H), 4.29 (s, 1H), 4.81 (br s, 1H), 5.36 (br s, 1H), 5.55 (br s, 1H), 6.01 (qd, J = 13, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.65, 20.47, 34.55, 53.51, 59.75, 63.07, 73.70, 75.46, 123.90, 127.60, 138.66, 139.51, 166.97; IR (thin film, NaCl plate) 1056, 1161, 1232, 1713, 2830−2930, 3050−3150 cm^{-1}; HRMS (FAB) *m/z* 238.1443, calcd for $C_{13}H_{20}NO_3$ 228.1443 (M^+H); $[\alpha]^{20}_D = +53.5°$ (*c* 0.77 mg/mL, $CDCl_3$).

Preparation of (+)-Latifoline (1). A solution of (+)-latifolic acid (35 mg, 0.2 mmol) in acetone (0.5 mL) was treated with carbonyldiimidazole (33 mg, 0.2 mmol). After 5 min, the solvent was evaporated under vacuum and the residue dissolved in chloroform (2 mL). This solution was added in four portions, over 20 h, to a solution of **16** (47 mg, 0.2 mmol) in

chloroform (3 mL). After the last addition, the mixture was stirred for an additional 5 h and then diluted to 8 mL with chloroform. The solution was washed with saturated aqueous $CuSO_4$, saturated $NaHCO_3$, and brine. After the solution was dried over 4 Å molecular sieves, the solvent was removed in vacuo. Preparative thin-layer chromatography (silica gel, MeOH) produced pure (+)-latifoline (35 mg, 45% yield) as a white crystalline solid: mp 101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J = 7.2 Hz, 3H), 1.27 (d, J = 6.7 Hz, 3H), 1.80 (quintet, J = 1.6 Hz, 3H), 1.95 (dq, J = 6.4, 1.6 Hz, 3H), 2.12 (m, 2H), 2.66−2.71 (m, 1H), 2.96 (q, J = 1.72 Hz, 1H), 3.33−3.4 (m, 2H), 3.95 (d, J = 15 Hz, 1H), 4.3 (br s, 1H), 4.40 (q, J = 6.4 Hz, 1H), 4.72 (d, J = 14 Hz, 1H), 4.87 (d, J = 14 Hz, 1H), 5.42 (br s, 1H), 5.83 (br s, 1H), 6.08 (q, J = 6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.38, 13.53, 15.83, 20.60, 34.56, 45.52, 53.96, 63.12, 63.69, 73.68, 76.02, 79.51, 83.39, 127.56, 128.76, 131.95, 139.04, 167.02, 171.39, 174.47; IR (thin film, NaCl plate) 1147 (s), 1231 (s), 1712 (s), 1747 (s), 1784 (s), 2850−2980 (m) cm^{-1}; HRMS (FAB) m/z 394.1866, calcd for $C_{20}H_{28}NO_7$ 394.1865 (M^+H); $[\alpha]_D$ = +54.2° (c 0.5, $CDCl_3$).

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Supporting Information Available: Experimental procedure for preparing retronecine from commercially available monocrotaline, as well as copies of the ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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