Asymmetric total synthesis of (+)-.DELTA.9(12)-capnellene

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Asymmetric Total Synthesis of (+)-$\Delta^{9(12)}$-Capnellene†

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The first asymmetric total synthesis of the unnatural enantiomer of (−)-$\Delta^{9(12)}$-capnellene has been achieved in 14.1% overall yield. The synthesis is based on the chiral nonracemic bicyclic lactam **15** derived from inexpensive (*S*)-valinol and levulinic acid. The goal of the synthesis, which was accomplished, was to reach the intermediate **13**, originally reported in racemic form, and carry out the last step to the title compound.

In our continuing studies on the use of chiral nonracemic bicyclic lactams of the type **1** (Chart I), we have to date successfully prepared a number of chiral cycloenones **2**[1] and **3**[2] as well as a number of complex products. The latter have ranged in type from alkaloids (mesembrine[3]) **4**, insect pheromones (grandisol[4]) **5**, insecticides (deltamethrin[5]) **6**, to plant growth regulators (abscisic acid[6]) **7**, sesquiterpene natural products (α-cuparenone,[7] **8**; silphiperfolene,[8] **9**), and the key precursor **10** to aspidospermine.[9] In addition, several novel carbocyclic systems (e.g., **11**), and chiral cyclopropanes have also been accessed[10] by using this versatile methodology.

We now report further progress based on the bicyclic lactams **1** by describing our asymmetric route to the unnatural enantiomer of capnellene **12**. The natural product (−)-**12** is found in the soft coral *Capnella imbricata* (Quoy and Gaimard, 1833) and is believed to be the biosynthetic precursor to the capnellane family of nonisoprenoid sesquiterpenes.[11a] These compounds display biological activities similar to those of their terrestial counterparts, the hirsutanes, which possess antibacterial and antitumor properties.[11b] The capnellane family seemingly serves as a chemical defense agent within the coral reef biomass toward algae and microbial growth and to prevent larvae settlement.[12]

The interest in these substances has provoked a large number of synthetic studies and has resulted in no less than 13 *racemic* total syntheses from a wide range of laboratories.[13] Our plan to reach the title compound **12** focused on the beautiful racemic route described by Curran and Chen[14] in 1985, which involved the radical cyclization of **13** (Scheme I). We felt that the chiral bicyclic lactam chemistry should allow interception of this route at the stage of **13**, utilizing as starting material the appropriately substituted quaternary substituted lactam **14**. Once reached in enantiomeric form, we hoped to complete the synthesis as described by Curran.

Starting from the readily available bicyclic lactam **15**[8] (Scheme II), deprotonation at the α-position using LDA–DMPU followed by addition of prenyl iodide gave the alkylated material **16** and **17** in 80% yield as a 3:2 mixture. This ratio, of course, is of no consequence since addition of LDA in the next step generates the planar enolate. Nevertheless, the mixture of **16** and **17** was conveniently separated via chromatography for characterization purposes. Repeating the enolization step as above and introduction of methyl iodide gave the quaternary substituted products **18** and **19** in 93% yield as a 91:9 mixture with the *endo*-methyl derivative **18** predominating.[15] Flash chromatography afforded pure **18** in 84% yield. An effort was also made to reach the reverse-substituted diastereomer **19** as the major product. By metalating **1** and

† This paper is dedicated to the memory of a dear friend and colleague, John K. Stille, whose untimely death on July 19, 1989, will be a great loss to chemistry.

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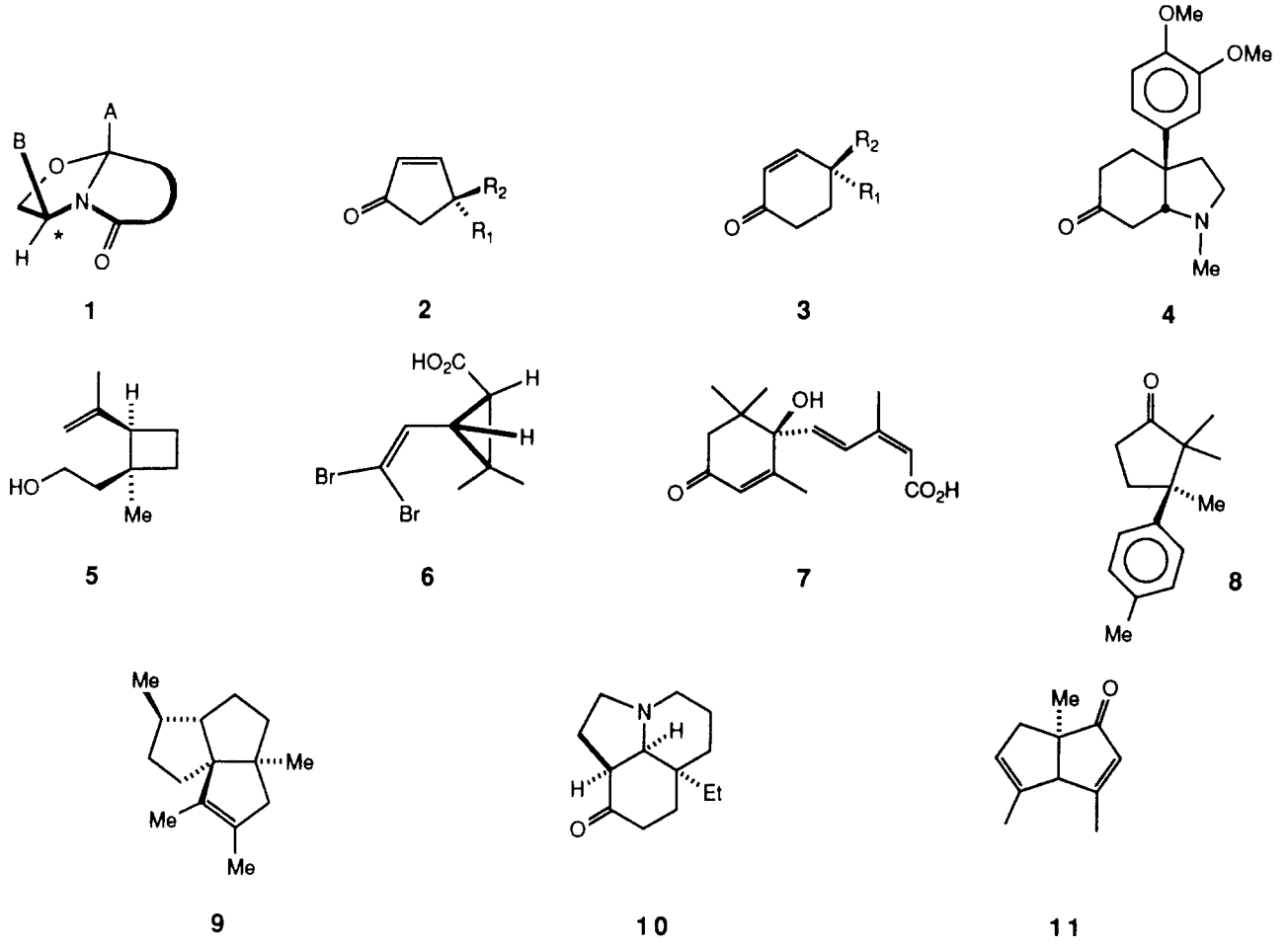
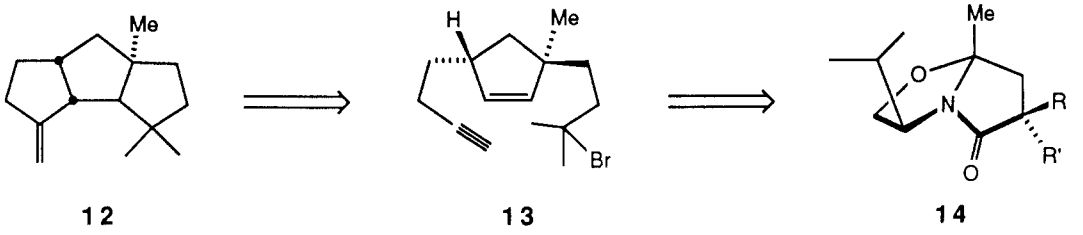
Chart I



Scheme I



alkylating initially with methyl iodide and then with prenyl iodide, the ratio of **19**:**18** we obtained was a disappointing 3:2. The major problem was found to be the sluggish alkylation rate of the chiral enolate with prenyl iodide at −80 to −100 °C. Most of the alkylation therefore occurred at −30 to 0 °C, which severly affected the stereoselectivity. The reverse diastereomer **19** was nevertheless cleanly separated and accompanied **18** in parallel synthetic sequence.

The pure diastereomer **18** was ozonized in excellent yield to the ketone **20**, which was then protected as the ketal **21** under the usual conditions. Reduction of the lactam carbonyl with $Na[Al(MeOCH_2CH_2O)_2H_2]$ followed by hydrolytic cleavage gave the keto aldehyde **22**, which was immediately treated with alkali–ethanol to give the cyclopentenone (*R*)-**23**. The latter was obtained in 78% yield from the lactam ketal **21**. On the basis of the diastereomeric purity of the lactams, which was determined to be virtually complete (HPLC, NMR), it may be safely assumed that the enantiomeric purity of the cyclopentenone was also very high (>99%).

For completion we also carried the diastereomeric lactam **19** on to the enantiomeric keto aldehyde, (*S*)-**22**, and ultimately to the cyclopentenone, (*S*)-**23**, which was identical in all respects with (*R*)-**23**, except for the sign of rotation.

Proceeding on to reach the Curran intermediate **13**, we next reduced the cyclopentenone (*R*)-(+)-**23** with sodium borohydride in the presence of $CeCl_3$ at 0 °C to obtain a 55:45 mixture of carbinols **24** and **25** in 92% combined yield, which were readily separated by flash chromatography into pure α- and β-alcohols. Each isomer was converted to the same key intermediate **27** by the route shown in Scheme III. The β-carbinol **24** was inverted to the α-carbinol **26** by the Mitsunobu procedure[16] and then subjected to retentive displacement[17] using sodiodimethyl malonate catalyzed by Pd(0), which furnished the diester **27** in 87% yield. Alternatively, the α-hydroxy derivative **25** was transformed into the allylic carbonate **28** and once

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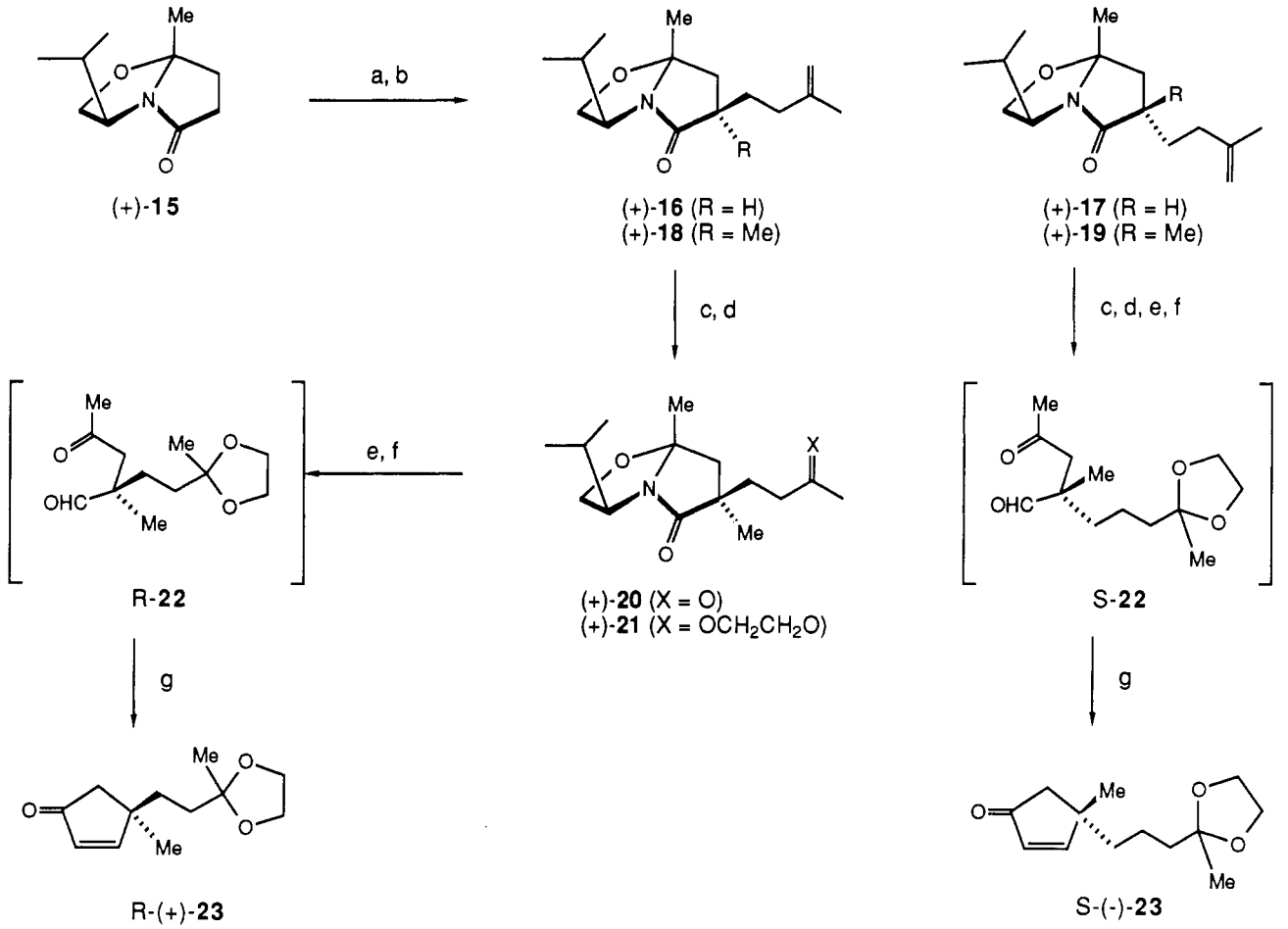
Scheme II[a]



[a] (a) LDA, DMPU, prenyl iodide, THF, −78 to −30 °C, 1 h. (b) LDA, DMPU, CH_3I, THF, −100 to −78 °C, 1 h. (c) 1. O_3, CH_2Cl_2/MeOH (1:1), −78 °C, 5 min; 2. Me_2S/H_2O, 25 °C, 4 h. (d) Ethylene glycol, *p*-TsOH, toluene, reflux, 45 min. (e) RED-Al (4 equiv), THF, −30 °C, 20 h. (f) 1 M aqueous $Bu_4NH_2PO_4/CH_2Cl_2$ (1:1) 25 °C, 7 days, or 1 M aqueous $Bu_4NH_2PO_4$, reflux, 2 h. (g) KOH, THF, 25 °C, 2 h.

again subjected to the Pd-catalyzed displacement. There was obtained the identical product **27** in 90% yield. Although both Pd-catalyzed acyl displacements are reported to proceed with a high degree of selectivity (retention), we did observe a small quantity of the inverted product (NMR). To unequivocally establish the stereochemistry of the displacements in **26** and **28**, we prepared the other epimer of **27**, namely, **29**. The latter was readily reached by transforming the β-hydroxy derivative **24** to its allylic carbonate and displacement with Pd(0) and dimethyl malonate as above. From NOE data, it was clearly confirmed that the stereochemistry of **27** is correct as shown and **29** was also consistent with the NOE experiments (see Experimental Section).

With the correct stereochemistry for the cyclopentene **27** in place, we proceeded to the next intermediate by the Krapcho carbodemethoxylation,[18] furnishing the ester **30** (Scheme IV). This was accomplished by treating the malonate with sodium chloride in DMSO–H_2O and heating for an hour. In this manner, the ester **30** was obtained in 92% yield. Reduction with lithium aluminum hydride gave the carbinol **31**, and transformation to the mesylate **32** was performed with methanesulfonyl chloride in pyridine. Treatment of the latter with sodium iodide in acetone then produced the iodide **33** in 90–93% overall yield from the ester **30**. To elongate the chain to provide the proper number of carbon atoms and also to introduce the alkynyl unit present in the Curran intermediate, the iodide **33** was treated with lithio acetylide–ethylenediamine complex[19] and furnished the alkyne **34** in 86% yield. Removal of the ketal moiety was next performed using toluenesulfonic acid in acetone, and the resulting methyl ketone **35** was treated with methylmagnesium chloride to give the tertiary alcohol **36**. This alcohol was spectroscopically identical (IR, ^1H NMR, ^{13}C NMR) with the racemic material.[14] The completion of the capnellene synthesis now followed the Curran route to intermediate **13**, which was readily obtained in 96% yield by treating the carbinol with trimethylsilyl bromide. Comparison of spectral properties of this chiral nonracemic bromide with those of racemic material showed them to be identical. Radical cyclization of **13** was performed using AIBN with tri-*n*-butylstannane in refluxing benzene to afford the title compound **12** in 58% yield. The material was identical in all respects with a sample kindly supplied by Professor Curran except for those originating from chiroptical properties. The optical rotation of the synthetic material ($[\alpha]_D$ +149°) was well within the limits of polarimetric error for the reported value[11] of the natural material ($[\alpha]_D$ −145°). These comparisons of the optical rotations are consistent with the diastereomeric purity of the bicyclic lactam **18**, which we had determined to be greater than 99%. Also the sign of the rotation implies that we reached the unnatural enantiomer of capnellene, and this also is

(18) Krapcho, A. P. *Synthesis* **1982**, *805*, 893.

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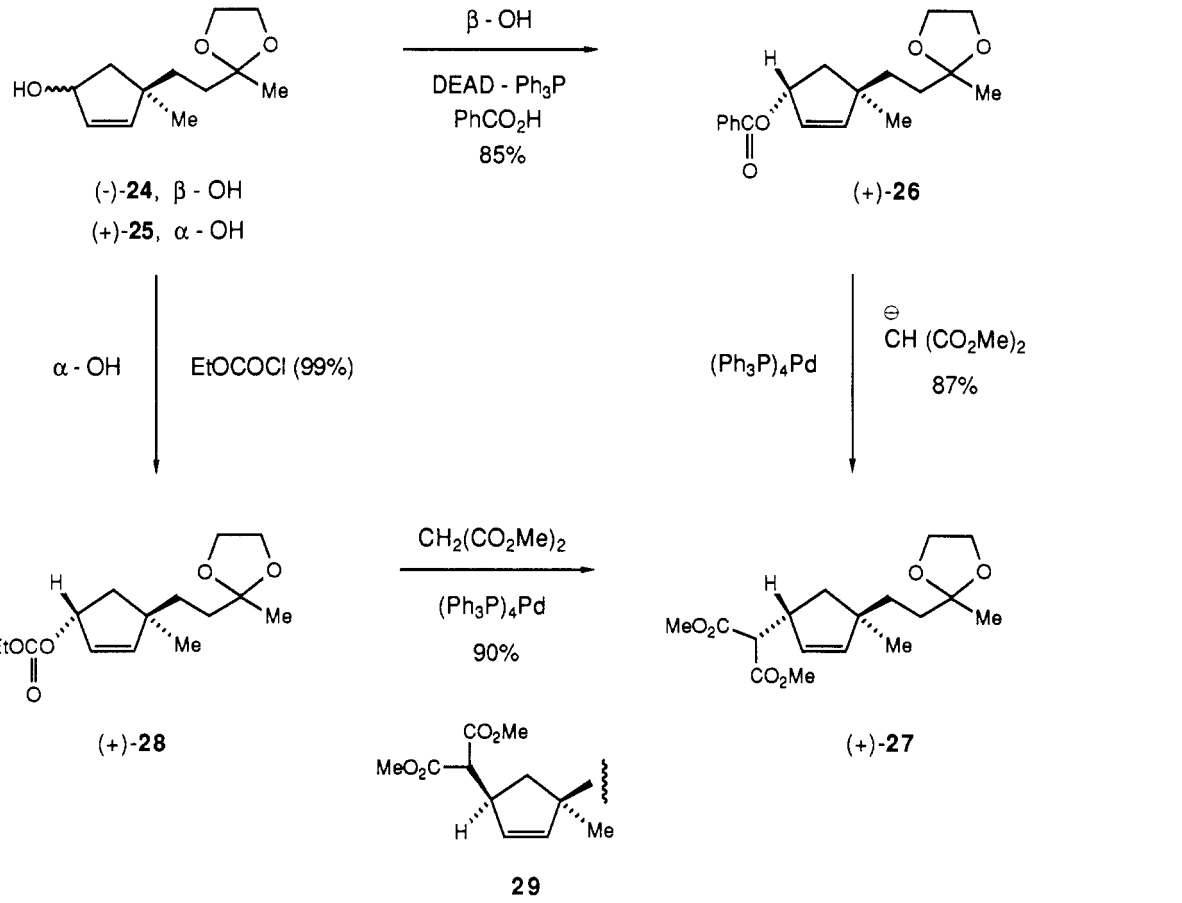
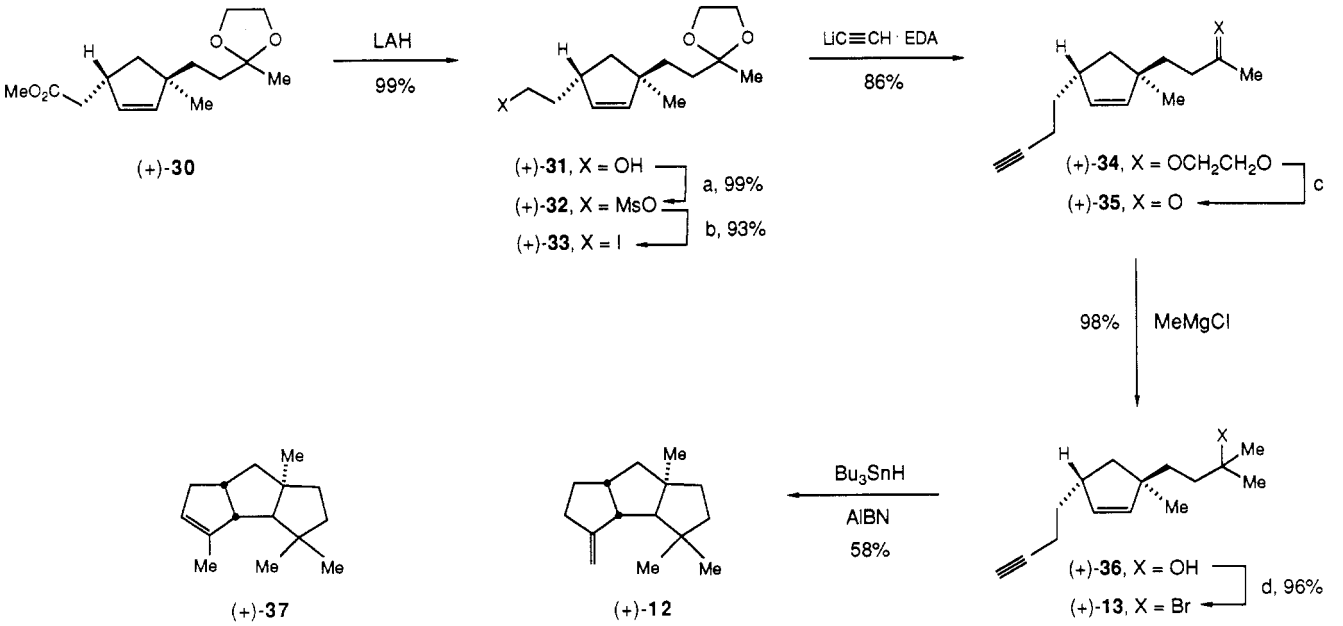
Scheme III



Scheme IV[a]



[a] (a) MsCl, pyridine, 0 → 25 °C. (b) NaI (excess), acetone, reflux. (c) TsOH, acetone, reflux. (d) TMSBr, CH_2Cl_2, room temperature.

consistent with the endo entry of the methyl iodide in the alkylation of **16**.

During the course of isolation of (+)-$\Delta^{9(12)}$-capnellene (**12**), we also found that use of activated silica gel (Aldrich, silica catalyst support grade 951) gave complete rearrangement to the endocyclic isomer **37**, which has been prepared earlier by Pattenden[13c] and Fujita.[13d] To avoid this rearrangement, it was necessary to chromatograph **12** by using nonactivated silica gel (Amicon, Matrex SilicaSi, 20–45 μm). In summary, we have accomplished the first asymmetric synthesis of this natural product (as its unatural enantiomer) in 20 steps and in 14.1% overall yield from commercially available starting materials. As mentioned above, there have been 13 total syntheses[13] of $\Delta^{9(12)}$-capnellene, all in racemic form, and involving a wide range of elegant chemistry. The number of steps (from

commercially available starting materials) has ranged from 7 to 24 with overall yields ranging from 0.6% to 14.1% (this study). It should also be noted that (*S*)-**23**, obtainable as the major enantiomer by starting with (−)-**15** (from (*R*)-valinol), would undoubtedly afford the (−)-capnellene, the natural enantiomer.

Experimental Section

General Procedures. All solvents were dried and stored over molecular sieves (3A) or dried directly before use. All reactions were carried out under a blanket of argon. During the workup, all extracts were dried over magnesium sulfate prior to evaporation of the solvents in vacuo. Chromatography was performed using Amicon, Matrex SilicaSi, 20–45 μm. Infrared spectra were all taken on neat material and ^{1}H NMR spectra were taken in $CDCl_3$ at 200, 270, or 300 MHz (coupling constants are given in hertz). ^{13}C NMR spectra were taken in $CDCl_3$ at 75.4 MHz with chemical shifts in δ relative to TMS as an internal standard. Multiplicities are from INEPT or DEPT experiments.

(3*S*,6*R*,7a*R*)- and (3*S*,6*S*,7a*R*)-3-Isopropyl-7a-methyl-6-(3-methyl-3-butenyl)-5-oxo-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole ((+)-16 and (+)-17). To a solution of 3.27 mmol of LDA and 3.27 mmol of *N*,*N*′-dimethylpropyleneurea (DMPU) in 10 mL of THF was added dropwise 500 mg (2.73 mmol) of (+)-**15**[8] (neat) at −78 °C. The solution was allowed to warm slowly to 0 °C and was stirred at this temperature for 30 min. After recooling to −78 °C, 614 mg (3.27 mmol) of prenyl iodide was added slowly. The reaction mixture was kept at −78 °C for 30 min, allowed to warm to 0 °C for an additional 30 min, cooled again to −78 °C, and quenched with acetic acid. Water was added, and the mixture extracted with ether. The extracts were washed with saturated $NaHCO_3$, water, and brine. Chromatography (ether–hexanes 1:10) gave 318 mg of (+)-**16** and 223 mg of (+)-**17**; total yield 541 mg, 79%.

Physical data for (+)-**17**: $[\alpha]^{20}_D$ +70.6° (*c* 0.50, $CHCl_3$); IR 3070, 1710, 1645 cm^{-1}; ^{1}H NMR δ 4.74–4.70 (m, 2 H), 4.15, 3.86 (AB portion of ABX, J_{AB} = 8.7, J_{AX} = 7.4, J_{BX} = 6.3, 2 H), 3.66–3.54 (m, 1 H), 2.85–2.75 (m, 1 H), 2.38, 1.79 (AB portion of ABX, J_{AB} = 12.5, J_{AX} = 8.3, J_{BX} = 12.0, 2 H), 2.11–2.02 (m, 3 H), 1.72 (s, 3 H), 1.68–1.60 (m, 1 H), 1.49–1.40 (m, 4 H, therein 1.47 (s, 3 H)), 1.02 (d, *J* = 6.6, 3 H), 0.89 (d, *J* = 6.6, 3 H); ^{13}C NMR δ 179.47, 144.87 (2 s), 110.41 (t), 97.38 (s), 70.81 (t), 61.06, 43.46 (2 d), 41.91, 35.18 (2 t), 33.35 (d), 28.41 (t), 24.77, 22.15, 20.40, 18.60 (4 q). Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.56; H, 9.96; N, 5.77.

Physical data for (+)-**16**: $[\alpha]^{20}_D$ +32.7° (*c* 0.71, $CHCl_3$); IR (neat) 3070, 1710, 1650 cm^{-1}; ^{1}H NMR δ 4.74–4.71 (m, 2 H), 4.17, 3.78 (AB portion of ABX, J_{AB} = 8.6, J_{AX} = 7.8, J_{BX} = 6.9, 2 H), 3.65–3.52 (m, 1 H), 2.61–2.52 (m, 1 H), 2.42, 1.85 (AB portion of ABX, J_{AB} = 13.6, J_{AX} = 10.2, J_{BX} = 4.0, 2 H), 2.15–1.96 (m, 3 H), 1.77–1.41 (m, 3 H, therein 1.73 (s, 3 H), and 1.48 (s, 3 H)), 1.05 (d, *J* = 6.4 3 H), 0.88 (d, *J* = 6.5, 3 H); ^{13}C NMR δ 182.87, 144.58 (2 s), 110.49 (t), 98.67 (s), 70.31 (t), 62.45, 43.59 (2 d), 38.33, 35.29 (2 t), 33.90 (d), 31.02 (t), 25.65, 22.26, 20.68, 18.84 (4 q). Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.58; H, 10.02; N, 5.38.

(3*S*,6*R*,7a*R*)- and (3*S*,6*S*,7a*R*)-3-Isopropyl-6,7a-dimethyl-6-(3-methyl-3-butenyl)-5-oxo-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole ((+)-8 and (+)-19). Starting with a Mixture of (+)-16 and (+)-17. To a solution of 6.0 mmol of LDA and 6.0 mmol of DMPU in 50 mL of THF was added dropwise 1.00 g (4.00 mmol) of a mixture of **16**–**17** (neat) at −78 °C. The solution was allowed to warm slowly to 0 °C and was stirred at this temperature for 30 min. After cooling to −100 °C, 0.76 mL (12.0 mmol) of iodomethane was added slowly. The reaction mixture was kept at −100 °C for 30 min, allowed to warm to 0 °C for an additional 30 min, cooled again to −100 °C, and quenched with acetic acid. Water was added, and the solution extracted with ether. The extracts were washed with saturated $NaHCO_3$, water, and brine. Chromatography (ether/hexanes 1:10) gave 83 mg of (+)-**19** (9%) and 893 mg of (+)-**18** (84%).

Physical data for (+)-**19**: $[\alpha]^{20}_D$ +66.0° (*c* 1.38, $CHCl_3$); IR 3070, 1710, 1650; ^{1}H NMR δ 4.67 (m apparent d, 2 H), 4.17, 3.77 (AB portion of ABX, J_{AB} = 8.6, J_{AX} = 7.8, J_{BX} = 6.9, 2 H), 3.64–3.51 (m, 1 H), 2.24, 1.94 (AB, J_{AB} = 13.5, 2 H), 2.14–1.16 (m, 15 H, therein B portion of previously described AB), 1.71 (s, 3 H), 1.49 (s, 3 H), 1.30 (s, 3 H)), 1.04 (d, *J* = 6.6, 3 H), 0.87 (d, *J* = 6.6, 3 H); ^{13}C NMR δ 183.85, 145.57 (2 s), 109.82 (t), 96.67 (s), 70.45 (t), 61.67 (d), 47.42 (s), 46.00, 36.50 (2 t), 34.12 (d), 32.51 (t), 25.88 (q, 2 c), 22.52, 20.66, 18.90 (3 q); MS (Cl), 266 (M + 1). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.35; H, 10.01; N, 5.40.

Physical data for (+)-**18**: $[\alpha]^{20}_D$ +17.4° (*c* 0.92, $CHCl_3$); IR 3075, 1715, 1650 cm^{-1}; ^{1}H NMR δ 4.71–4.69 (m, 2 H), 4.19, 3.76 (AB portion of ABX, J_{AB} = 8.5, J_{AX} = 7.7, J_{BX} = 7.1, 2 H), 3.66–3.58 (m, 1 H), 2.16, 2.06 (AB, J_{AB} = 13.7, 2 H), 2.09–1.97 (m, 4 H, therein B portion of previous described AB), 1.74–1.62 (m, 6 H, therein 1.73 (s, 3 H)), 1.49 (s, 3 H), 1.17 (s, 3 H), 1.05 (d, *J* = 6.4, 3 H), 0.88 (d, *J* = 6.4, 3 H); ^{13}C NMR δ 184.34, 145.14 (2 s), 109.86 (t), 96.54 (s), 70.12 (t), 62.18 (d), 46.99 (s), 46.01, 37.74 (2 t), 34.00 (d), 32.71 (t), 25.15, 24.36, 22.46, 20.68, 18.79 (5 q); MS (Cl), 266 (M + 1). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.14; H, 9.99; N, 5.21.

(3*S*,6*R*,7a*R*)-3-Isopropyl-6,7a-dimethyl-6-(3-oxobutyl)-5-oxo-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole ((+)-20). Through a solution of 200 mg (0.75 mmol) of (+)-18 in CH_2Cl_2/MeOH (2:1) at −78 °C was passed ozone until the blue color persisted. Excess ozone was removed with a stream of argon. To reduce the peroxide, 6 mL of dimethyl sulfide was added, and after 1 h, 1 mL of water was added. The mixture was allowed to warm to 23 °C and stirred 3–4 h at this temperature. After concentration in vacuo the residue was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine. Chromatography (ether/hexanes 1:2) gave 197 mg (98%) of (+)-**20**: $[\alpha]^{20}_D$ +25.7° (*c* 0.98, $CHCl_3$); IR 1710 cm^{-1}; ^{1}H NMR δ 4.20, 3.77 (AB portion of ABX, J_{AB} = 8.7, J_{AX} = 7.7, J_{BX} = 7.0, 2 H), 3.63–3.51 (m, 1 H), 2.59–2.49 (m, 2 H), 2.16 (s, 3 H), 2.10 (s, 2 H), 2.03–1.58 (m, 3 H), 1.50 (s, 3 H), 1.14 (s, 3 H), 1.03 (d, *J* = 6.4, 3 H), 0.88 (d, *J* = 6.7, 3 H); ^{13}C NMR δ 207.50, 184.34, 96.54 (3 s), 70.07 (t), 61.83 (d), 47.24 (t), 46.09 (s), 38.57 (t), 33.78 (d), 33.07 (t), 29.76, 25.18, 23.63, 20.54, 18.55 (5 q); MS (Cl), 268 (M + 1). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.11; H, 9.64; N, 5.20.

(3*S*,6*R*,7a*R*)-6-(3,3-Ethylenedioxybutyl)-3-isopropyl-6,7a-dimethyl-5-oxo-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole ((+)-21). A mixture of 910 mg (3.41 mmol) of (+)-**20**, 0.95 mL (17.0 mmol) of ethylene glycol, and 10 mg of *p*-TsOH in 50 mL toluene was heated to reflux for 30 min, and the condensates were dried by passing through molecular sieves (3A). The reaction mixture was poured on an ice/saturated aqueous $NaHCO_3$ mixture, the layers were separated, and the aqueous phase was extracted with ether. The combined organic layers were washed with water and brine. Chromatography (ether/hexanes 1:3) gave 1.00 g (95%) of (+)-**21**: $[\alpha]^{20}_D$ +15.5° (*c* 1.13, $CHCl_3$); IR 1710 cm^{-1}; ^{1}H NMR δ 4.19, 3.76 (AB portion of ABX, J_{AB} = 8.6, J_{AX} = 7.7, J_{BX} = 7.0, 2 H), 3.97–3.90 (m, 4 H), 3.65–3.53 (m, 1 H), 2.13, 2.04 (AB, J_{AB} = 13.9, 2 H), 1.73–1.60 (m, 5 H), 1.48 (s, 3 H), 1.32 (s, 3 H), 1.14 (s, 3 H), 1.04 (d, *J* = 6.7, 3 H), 0.88 (d, *J* = 6.6, 3 H); ^{13}C NMR δ 184.32, 109.56, 96.56 (3 s), 70.19 (t), 64.49 (t, 2 C), 62.10 (d), 46.70 (s), 46.16 (t), 34.00 (d), 33.88, 33.53 (2 t), 25.20, 24.09, 23.68, 20.69, 18.82 (5 q).

(*R*)-4-(3,3-Ethylenedioxybutyl)-4-methyl-2-cyclopenten-1-one (*R*-(+)-23). To a solution of 236 mg (0.759 mmol) of (+)-21 in 10 mL of THF was added 0.90 mL (3.04 mmol) of Red-Al (3.4 M in hexane) at −78 °C. The solution was warmed to −30 °C for 20 h, MeOH was added, and the solvents were evaporated. The residue was dissolved in ether and washed with 5% aqueous NaOH, water, and brine. The crude carbinolamine (312 mg) was dissolved in 10 mL of CH_2Cl_2 and 10 mL of 1 M $Bu_4NH_2PO_4/H_2O$, and the mixture was stirred vigorously at room temperature for 7 days. The aqueous phase was extracted with Et_2O, and the combined organic layers were washed with water and brine. Evaporation of the solvent gave crude ketoaldehyde **22** (157 mg), which was dissolved in 5 mL of THF and treated with 5 drops of 1 M KOH in ethanol at room temperature for 2.5 h, and then the THF was evaporated. The residue was dissolved in ether and washed with water and brine. Chromatography (Et_2O/hexanes 1:2) gave 124 mg (78%) of (+)-**23**: $[\alpha]^{20}_D$ +58.6° (*c*, 1.44, $CHCl_3$); IR 3074, 1713, 1672 cm^{-1}; ^{1}H NMR δ 7.42 (d, *J* = 5.6, 1 H), 6.04 (d, *J* = 5.6, 1 H), 3.98–3.90 (m, 4 H), 2.32, 2.12 (AB, J_{AB} = 18.7, 2 H), 1.64–1.55 (m, 4 H), 1.29 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR

δ 209.58 (s), 172.61, 131.93 (2 d), 109.55 (s), 64.63 (t, 2 C), 47.45 (t), 44.34 (s), 34.43, 34.03 (2 t), 26.24, 23.83 (2 q). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.39; H, 8.78.

(*S*)-4-(3,3-Ethylenedioxybutyl)-4-methyl-2-cyclopenten-1-one (*S*-(−)-23). In a fashion similar to that described for (*R*)-(+)-**23**, the bicyclic lactam (+)-**19** was subjected to the same series of reactions (ozonolysis, ketalization, reduction, and hydrolysis). The spectral properties of (*S*)-(−)-**23** were identical with those obtained for (*R*)-(+)-**23** except for rotation. The data for this series are included in the supplementary material (see the paragraph at the end of the paper.

(1*S*,4*R*)- and (1*R*,4*R*)-4-(3,3-Ethylenedioxybutyl)-4-methyl-2-cyclopenten-1-ol ((−)-24 and (+)-25). A solution of 600 mg (2.86 mmol) of (+)-**23** and 1.06 g (2.86 mmol) of $CeCl_3$ in 20 mL of methanol was cooled to 0 °C, and 109 mg (2.86 mmol) of $NaBH_4$ was added. The solution was quenched after 5 min with 2 mL of acetic acid, water was added, and the mixture was extracted with ether. Chromatography (ether/hexanes 1:2) gave 262 mg (43%) of (+)-**25** and 307 mg (51%) of (−)-**24**; total yield 569 mg (94%).

Physical data for (−)-**24**: $[\alpha]^{20}_D$ −22.1° (*c* 1.26, $CHCl_3$); IR 3416 (br), 3050, 1619 (w) cm^{-1}; ^1H NMR δ 5.75–5.66 (m, 2 H), 4.89 (br s, 1 H), 3.96–3.90 (m, 4 H), 2.05 (dd, *J* = 13.7, 7.5, 1 H), 1.74–1.43 (m, 6 H), 1.31 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR δ 209.33 (s), 143.83, 143.22, 131.78, 131.35 (4 d), 110.12 (s), 77.30, 77.02 (2 d), 64.61 (t, 2 C), 47.61 (s), 46.89, 46.33, 39.90, 35.92, 34.98, 34.76, (6 t), 30.01, 27.57, 27.20, 23.81 (4 q).

Physical data for (+)-**25**: $[\alpha]^{20}_D$ +89.5° (*c* 0.96, $CHCl_3$); IR: 3417 (br), 3050, 1620 (w) cm^{-1}; ^1H NMR δ 5.71 (m apparent s, 2 H), 4.86–4.82 (m, 1 H), 3.95–3.90 (m, 4 H), 2.17 (dd, *J* = 13.8, 7.5, 1 H), 1.72–1.38 (m, 6 H), 1.29 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR δ 143.85, 131.49 (2 d), 110.08 (s), 77.57 (d), 64.61 (t, 2 C), 47.84 (s), 46.98, 35.42, 34.70 (3 t), 28.60, 23.78 (2 q). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.92; H, 9.67.

(1*R*,4*R*)-*O*-Benzoyl-4-(3,3-ethylenedioxybutyl)-4-methyl-2-cyclopenten-1-ol ((+)-26). To a solution of 270 mg (1.27 mmol) of (−)-**24**, 667 mg (2.55 mmol) of Ph_3P, and 311 mg of (2.55 mmol) benzoic acid in 10 mL of THF was added dropwise at room temperature a solution of 443 mg (2.55 mmol) of diethylazodicarboxylate (DEAD) in 3 mL of THF. The solvent was evaporated after 1.5 h, and the residue dissolved in dichloromethane and washed with saturated aqueous $NaHCO_3$ and brine. Chromatography (ether/hexanes 1:4) gave 337 mg (84%) of (+)-**26**: $[\alpha]^{20}_D$ +157.8° (*c* 0.8, $CHCl_3$); IR 3063, 3037, 1968 (w), 1911 (w), 1714, 1602, 1585 cm^{-1}; ^1H NMR δ 8.01 (dd, *J* = 8.3, 1.3, 2 H), 7.56–7.50 (m, 1 H), 7.44–7.38 (m, 2 H), 5.89–5.79 (m, 2 H), 3.95–3.90 (m, 4 H), 2.25 (dd, *J* = 14.2, 7.6, 1 H), 1.72 (dd, *J* = 14.2, 3.4, 1 H), 1.65–1.42 (m, 4 H), 1.30 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR δ 166.40 (s), 146.45, 132.73 (2 d), 129.52 (d, 3 C), 128.25 (d, 2 C), 127.44 (d), 110.13 (s), 80.66 (d), 64.63 (t, 2 C), 47.85 (s), 43.25, 35.14, 34.68 (3 t), 27.90, 23.82 (2 q).

(1*R*,4*R*)-*O*-Ethoxycarbonyl-4-(3,3-ethylenedioxybutyl)-4-methyl-2-cyclopenten-1-ol ((+)-28). A solution of 20.0 mg (0.094 mmol) of (+)-**25** in 1 mL of CH_2Cl_2 was cooled to 0 °C. Pyridine (11 μL) and ethyl chloroformate (11 μL, 0.14 mmol) were added. After 20 min at ambient temperature it was quenched with ice water and extracted with ether. The extracts were washed with water and brine. Filtration through SiO_2 with ether gave 28.0 mg (100%) of (+)-**28**: $[\alpha]^{22}_D$ +115.2° (*c* 1.24, $CHCl_3$); IR 1738, 1256 cm^{-1}; ^1H NMR δ 5.85 (dd, *J* = 5.6 0.9, 1 H), 5.74 (dd, *J* = 5.6, 2.1, 1 H), 5.59–5.54 (m, 1 H), 4.18 (q, *J* = 7.1, 2 H), 3.97–3.87 (m, 4 H), 2.19 (dd, *J* = 14.3, 7.6, 1 H), 1.66 (dd, *J* = 14.3, 3.5, 1 H), 1.59–1.43 (m, 4 H), 1.30 (t, *J* = 7.1, 3 H), 1.29 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR δ 154.93 (s), 146.76, 126.93 (2 d), 109.95 (s), 83.60 (d), 64.61 (d, 2 C), 63.69 (t), 47.87 (s), 42.89, 35.16, 34.65 (3 t), 27.74, 23.23, 14.27 (3 q). Nuclear Overhauser data:

irradiation at δ	responsive signals (%)
5.59–5.54	5.74 (3.2), 2.19 (4.0)
2.19	5.59–5.54 (9.6), 1.66 (27.7)
1.66	2.19 (21.1), 1.29 (1.8)
1.29	5.85 (1.5), 1.66 (1.6)

Dimethyl [(3*R*,5*R*)-4-(3,3-Ethylenedioxybutyl)-4-methyl-2-cyclopenten-1-yl]propanedioate ((+)-27). Starting with (+)-26. A 0.2 M solution of dimethyl malonate sodium salt in THF (7.5 mL, 1.5 mmol) was added dropwise at room temperature to a solution of 337 mg (1.07 mmol) (+)-**26** and 10 mg of $(Ph_3P)_4Pd$ in 3 mL of THF. After 20 h at 30 °C saturated aqueous $NaHCO_3$ was added, THF removed, and the residue extracted with ether. Chromatography (ether/hexanes 1:4) gave 301.6 mg (87%) of (+)-**27** (contaminated with a small amount of **29**).

Starting with (+)-28. A solution of 31.2 mg (0.096 mmol) of (+)-**28**, 30 mg (0.188 mmol) of dimethyl malonate, and 10 mg of $(Ph_3P)_4Pd$ in 3 mL of THF was warmed to 40 °C for 2 h. Workup as above gave 27.9 mg (90%) of (+)-**27** $[\alpha]^{22}_D$ +80.7° (*c* 0.58, $CHCl_3$); IR 1755, 1737 cm^{-1}; ^1H NMR δ 5.58–5.52 (m, 2 H), 4.08–3.85 (m, 4 H), 3.74 (s, 6 H), 3.45–3.37 (m, 1 H), 3.26 (d, *J* = 10.0, 1 H), 2.03 (dd, *J* = 13.3, 7.2, 1 H), 1.64–1.25 (m, 8 H, therein 1.30 (dd, *J* = 13.3, 6.9), 1.27 (s)), 1.07 (s, 3 H); ^{13}C NMR δ 169.01 (s, 2 C), 141.73, 129.50 (2 d), 110.13 (s), 64.60 (t, 2 C), 57.52 (d), 52.35 (q, 2 C), 48.12 (s), 45.38 (d), 41.26, 35.36, 34.52 (3 t), 28.17, 23.81 (2 q). Nuclear Overhauser data:

irradiation at δ	responsive signals (%)
3.45–3.37	5.58–5.52 (3.8), 2.03 (3.4)
3.26	5.58–5.52 (2.5), 1.30 (4.5), 1.07 (0.5)
2.03	3.45–3.37 (7.5), 1.30 (22.1)
1.07	5.58–5.52 (2.3), 3.26 (0.7), 1.30 (2.3)

Dimethyl [(3*R*,5*S*)-4-(3,3-Ethylenedioxybutyl)-4-methyl-2-cyclopenten-1-yl]propanedioate ((+)-29). A solution of 28.0 mg (0.132 mmol) of (−)-**24** in 2 mL of CH_2Cl_2 was cooled to 0 °C. Pyridine (60 μL) and ethyl chloroformate (30 mg, 0.184 mmol) were added. After 20 min at ambient temperature the solution was quenched with ice water and extracted with ether. The extracts were washed with water and brine. Filtration through SiO_2 (ether) gave 43.7 mg (100%) of the β-carbonate *epi*-**28** which was used in the next step without further purification; ^1H NMR δ 5.85 (dd, *J* = 6.2, 0.7, 1 H), 5.71 (dd, *J* = 6.2, 2.1, 1 H), 5.66–5.60 (m, 1 H), 4.18 (q, *J* = 7.1, 2 H), 3.96–3.89 (m, 4 H), 2.10 (dd, *J* = 14.1, 7.7, 1 H), 1.76 (dd, *J* = 14.1, 4.2, 1 H), 1.70–1.34 (m, 4 H) 1.31 (s and t, *J* = 7.1, 6 H), 1.07 (s, 3 H).

A solution of 43.7 mg (0.132 mmol) of the above crude carbonate *epi*-**28**, 60 mg (0.375 mmol) of dimethyl malonate, and 10 mg of $(Ph_3P)_4Pd$ in 4 mL of THF was warmed to 40 °C for 2 h. Saturated aqueous $NaHCO_3$ was added, THF removed in vacuo, and the residue extracted with ether. Chromatography (ether/hexanes 1:4) gave 27.0 mg (63%) of **29** (contaminated with a small amount of (+)-**27**; IR 1732 (C=O); ^1H NMR δ 5.60 (dd, *J* = 5.6, 2.3, 1 H), 5.50 (dd, *J* = 5.6, 1.7, 1 H), 3.96–3.90 (m, 4 H), 3.74 (2 s, 6 H), 3.52–3.38 (m, 1 H), 3.25 (d, *J* = 10.0, 1 H), 1.86 (dd, *J* = 12.9, 7.8, 1 H), 1.56–1.40 (m, 5 H, therein 1.40 (dd, *J* = 12.9, 7.9)), 1.31 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR δ 169.01 (s, 2 C), 141.92, 129.14 (2 d), 110.12 (s), 64.60 (t, 2 C), 57.05 (d), 52.36 (q, 2 C), 48.07 (s), 44.51 (d), 41.13, 35.51, 34.69 (3 t), 26.13, 23.80 (2 q). Nuclear Overhauser data:

irradiation at δ	responsive signals (%)
3.52–3.38	5.50 (6.8), 1.86 (4.7)
3.25	5.50 (2.1), 1.40 (2.3)
1.86	3.52–3.38 (11.8), 1.40 (24.1), 1.02 (3.5)
1.02	5.60 (1.3), 3.52–3.38 (1.4), 1.86 (1.9)

Methyl (3*R*,5*S*)-4-(3,3-Ethylenedioxybutyl)-4-methyl-2-cyclopentene-1-acetate ((+)-30). A solution of 290 mg (0.895 mmol) of (+)-**27**, 0.2 mL of water, and 30 mg of sodium chloride in 10 mL of DMSO was heated to reflux for 1 h. The mixture was cooled to room temperature, poured into water, and extracted with dichloromethane. The extracts were washed with water and brine and filtered through SiO_2 (CH_2Cl_2) to give 221 mg (92%) of (+)-**30**: $[\alpha]^{22}_D$ +73.4° (*c* 1.23, $CHCl_3$); IR 3039, 1738 cm^{-1}; ^1H NMR δ 5.56–5.48 (m, 2 H), 3.96–3.89 (m, 4 H), 3.68 (s, 3 H), 3.13–3.08 (m, 1 H), 2.42, 2.29 (AB portion of ABX, J_{AB} = 15.1, J_{AX} = 7.2, J_{BX} = 8.1, 2 H), 2.04 (dd, *J* = 13.2, 8.3, 1 H), 1.64–1.31 (m, 4 H), 1.30 (s, 3 H), 1.21 (dd, *J* = 13.2, 6.7, 1 H), 1.08 (s, 3 H); ^{13}C NMR δ 137.28 (s), 140.43, 131.75 (2 d), 110.21 (s), 64.60 (t, 2 C), 51.44 (q), 48.28 (s), 43.22 (t), 42.02 (d), 41.10, 35.43, 34.57 (3 t), 28.40, 23.79 (2 q).

(3*R*,5*S*)-2-[4-(3,3-Ethylenedioxybutyl)-4-methyl-2-cyclopenten-1-yl]ethanol ((+)-31). To a cooled solution (0 °C) of

249 mg (0.929 mmol) of (+)-**30** in 10 mL of THF was added 36 mg (0.930 mmol) of $LiAlH_4$. The reaction mixture was allowed to warm to room temperature, and after 10 min it was quenched with a saturated aqueous Na/K tartrate solution. THF was evaporated, and the residue extracted with ether. Filtration through SiO_2 (ether) gave 128.9 mg (quantitative) of (+)-**31**, which was used in the next step without further purification. The physical properties were taken from a small purified sample (SiO_2, ether/hexanes 2:1); $[\alpha]^{22}_D$ +70.2° (*c* 1.28, $CHCl_3$); IR 3425, 3039, 1617 (w) cm^{-1}; ^1H NMR δ 5.56, 5.46 (AB portion of ABX, J_{AB} = 5.6, J_{AX} = 1.9, J_{BX} = 2.3, 2 H), 3.95–3.89 (m, 4 H), 3.70–3.65 (m, 2 H), 2.84–2.77 (m, 1 H), 1.98 (dd, *J* = 12.9, 8.2, 1 H), 1.77–1.31 (m, 6 H), 1.30 (s, 3 H), 1.19 (dd, *J* = 12.9, 6.9, 1 H), 1.08 (s, 3 H); ^{13}C NMR δ 139.51, 132.73 (2 d), 110.23 (s), 64.51 (t, 2 C), 61.69 (t), 48.04 (s), 43.51 (t), 42.13 (d), 39.79, 35.41, 34.54 (3 t), 28.38, 23.70 (2 q). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.87; H, 10.21.

(3*R*,5*S*)-3-(3,3-Ethylenedioxybutyl)-5-(2-(methanesulfonyloxy)ethyl)-3-methyl-1-cyclopentene ((+)-32). To an ice-cooled solution of 117.3 mg (0.489 mmol) of (+)-**31** in 1.0 mL of pyridine was added 0.10 mL (0.17 mmol) of methanesulfonyl chloride (neat). After stirring for 1 h at ambient temperature, it was treated with saturated aqueous $NaHCO_3$, and stirring continued for an additional hour. Extraction with ether and filtration through SiO_2 (ether) gave 172.0 mg (quantitative) of (+)-**32**. This material was used directly in the next step without further purification. Properties of crude mesylate: IR 3036, 1356, 1173 cm^{-1}; ^1H NMR δ 5.53 (br s, 2 H), 4.26 (t, *J* = 6.7, 2 H), 3.93 (br s, 4 H), 3.02 (s, 3 H), 2.88–2.79 (m, 1 H), 2.07–1.14 (m, 11 H, therein 1.30 (s)), 1.09 (s, 3 H).

(3*R*,5*S*)-3-(3,3-Ethylenedioxybutyl)-5-(2-iodoethyl)-3-methyl-1-cyclopentene ((+)-33). A solution of 172 mg (0.489 mmol) of (+)-**32** and 1.0 g of sodium iodide in 3 mL of acetone was heated to reflux for 1 h. After dilution with 5 mL of water, the acetone was evaporated in vacuo. Extraction with ether and filtration through SiO_2 (ether) gave 158.5 mg (93%) of **33**. This material was used in the next step without further purification. Spectral properties of the crude iodide: IR 3039, 1617 (w) cm^{-1}; ^1H NMR δ 5.54–5.45 (m, 2 H), 3.95–3.90 (m, 4 H), 3.21–3.15 (m, 2 H), 2.83–2.73 (m, 1 H), 1.99 (dd, *J* = 13.1, 8.2, 1 H), 1.82–1.31 (m, 6 H), 1.30 (s, 3 H), 1.14 (dd, *J* = 13.1, 6.7, 1 H), 1.07 (s, 3 H).

(3*R*,5*S*)-5-(3-Butynyl)-3-(3,3-ethylenedioxybutyl)-3-methyl-1-cyclopentene ((+)-34). A brown slurry of 6.3 mg (0.0686 mmol) of **33** in 0.2 mL of DMSO, after stirring for 30 min at room temperature, was cooled with ice, and water was added carefully. Extraction with dichloromethane and filtration through SiO_2 (CH_2Cl_2) gave 36.6 mg (86%) of (+)-**34**: $[\alpha]^{22}_D$ +86.6° (*c* 0.47, $CHCl_3$); IR 3305, 3040, 2118 cm^{-1}; ^1H NMR δ 5.55, 5.47 (AB portion of ABX, J_{AB} = 5.6, J_{AX} = 1.8, J_{BX} = 2.2, 2 H), 3.95–3.87 (m, 4 H), 2.84–2.77 (m, 1 H), 2.32–2.13 (m, 2 H), 2.01–1.93 (m, 2 H), 1.78–1.31 (m, 9 H), 1.30 (s, 3 h), 1.15 (dd, *J* = 13.1, 6.8, 1 H), 1.07 (s, 3 H); ^{13}C NMR δ 139.78, 132.34 (2 t), 110.26, 84.57 (2 s), 68.17 (d), 64.57 (t, 2 C), 48.11 (s), 44.75 (d), 43.13 (t), 35.58 (t, 2 C), 34.58 (t), 28.48, 23.76 (2 q), 16.95 (t).

(3*R*,5*S*)-5-(3-Butynyl)-3-methyl-3-(3-oxobutyl)-1-cyclopentene ((+)-35). A solution of 36.6 mg (0.148 mmol) of (+)-**34** and 10 mg of *p*-TsOH in 5 mL of acetone was heated to reflux for 6 h. Water was added, and acetone evaporated. Extraction and chromatography (semipreparative HPLC, EtOAc/hexanes 1:20) gave 26.8 mg (89%) of (+)-**35**: $[\alpha]^{22}_D$ +107.5° (*c* 0.80, $CHCl_3$); IR 3300, 3040, 2117, 1715, 1618 (w) cm^{-1}; ^1H NMR δ 5.56, 5.41 (AB portion of ABX, J_{AB} = 5.6, J_{AX} = 1.9, J_{BX} = 2.3, 2 H), 2.81–2.77 (m, 1 H), 2.38–2.31 (m, 2 H), 2.22–2.13 (m, 2 H), 2.11 (s, 3 H), 1.96–1.49 (m, 4 H), 1.15 (dd, *J* = 13.1, 6.9, 1 H), 1.06 (s 3 H); ^{13}C NMR δ 209.42 (s), 139.16, 132.97 (2 d), 84.41 (s), 68.29 (d), 48.09 (s), 44.76 (d), 43.03, 39.84, 35.45, 35.08 (4 t), 29.96, 28.45 (2 q), 16.91 (t). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.11; H, 10.14.

(3*R*,5*S*)-5-(3-Butynyl)-3-methyl-3-(3-hydroxy-3-methylbutyl)-1-cyclopentene ((+)-36). To a solution of 80.2 mg (0.392 mmol) of (+)-**35** in 4 mL of THF at 0 °C was added dropwise 0.20 mL (0.59 mmol) of a 3 M methylmagnesium chloride solution in ether (Aldrich). The reaction mixture was warmed to room temperature and quenched after 30 min with saturated aqueous Na/K tartrate solution. Extraction with ether and filtration through SiO_2 (ether) gave 94 mg (92% pure, quantitative yield) of (+)-**36** which was used without further purification in the next step. The spectroscopic data of a purified sample (SiO_2, ether/hexanes 1:2) were identical with those kindly provided by Professor Curran; IR 3377 (br), 3311, 3041, 2118 cm^{-1}; ^1H NMR δ 5.53, 5.46 (AB portion of ABX, J_{AB} = 5.6; J_{AX} = 1.8, J_{BX} = 2.2, 2 H), 2.81–2.76 (m, 1 H), 2.22–2.16 (m, 2 H), 1.95 (dd, *J* = 13.0, 8.2, 1 H), 1.92 (t, *J* = 2.6, 1 H), 1.69–1.18 (m, 7 H), 1.17 s, 6 H), 1.14 (dd, *J* = 13.0, 6.7, 1 H), 1.05 (s, 3 H); ^{13}C NMR δ 139.92, 132.27 (2 d), 84.54, 70.91 (2 s), 68.17 (d), 48.21 (s), 44.73 (d), 43.24, 38.97, 35.94, 35.56 (4 t), 29.21 (q, 2 C), 28.39 (q), 16.94 (t). The specific rotation for the present purified sample was determined as $[\alpha]$ = +94.3° (*c* = 0.90 in $CHCl_3$).

(3*R*,5*S*)-5-(3-Butynyl)-3-methyl-3-(3-bromo-3-methylbutyl)-1-cyclopentene ((+)-13). To a solution of 70.0 mg (92% pure, 0.292 mmol) of (+)-**36** in 10 mL of dichloromethane at room temperature was added 0.20 mL (1.27 mmol) of trimethylsilyl bromide. After stirring for 2 h, the solution was quenched with saturated aqueous $NaHCO_3$; $NaHSO_3$ was added, and the solution extraction with ether. Filtration through SiO_2 (ether) gave 79.0 mg (96%) of crude **13**. The spectroscopic data of crude material were identical with those supplied by Professor Curran; ^1H NMR δ 5.57, 5.47 (AB portion of ABX, J_{AB} = 5.7, J_{AX} = 1.8, J_{BX} = 2.1, 2 H), 2.86–2.77 (m, 1 H), 2.27–2.17 (m, 2 H), 2.00 (dd, *J* = 13.1, 8.1, 1 H), 1.94 (t, *J* = 2.5, 1 H), 1.82–1.40 (m, 12 H, therein 1.75, 1.74 (2 s)), 1.18 (dd, *J* = 13.1, 6.8, 1 H), 1.06 (s, 3 H); ^{13}C NMR δ 139.70, 132.54 (2 d), 84.52, 68.66 (2 s), 68.20 (d), 48.12 (s), 44.77 (d), 43.10, 42.84, 37.77, 35.57 (4 t), 34.25, 34.19, 28.49 (3 q), 16.95 (t).

(+)-$\Delta^{9(12)}$-Capnellene ((+)-12). To a solution of 79.0 mg (0.28 mmol) of crude (+)-**13** in 50 mL of benzene at reflux was added over 2 h via syringe pump a solution of 140 mg (0.477 mmol) of Bu_3SnH and 11.8 mg of AIBN in 2.8 mL of benzene. Reflux was continued for 3 h, and after cooling to room temperature 2 mL of 1 M Bu_4NF in water was added and stirred overnight. Extraction with pentanes and chromatography (pentanes) gave 33.2 mg of (+)-**12** (58%; 56% starting from tertiary alcohol (+)-**36**). The spectroscopic data (IR, ^1H and ^{13}C NMR) and chromatographic behavior (TLC, GC) of our (+)-**12** was identical with those of an authentic (synthetic) sample of (±)-**12** supplied by Professor Curran and those reported for the natural product; $[\alpha]^{22}_D$ +149° (*c* 0.10, $CHCl_3$); reported[11] $[\alpha]_D$ −145° (*c* 0.4, $CHCl_3$); IR 3069, 2927, 2864, 1651, 1457, 1374, 1364, 875 cm^{-1}; ^1H NMR δ 4.89–4.88 (m, 1 H), 4.78–4.76 (m, 1 H), 2.69–2.28 (m, 4 H), 1.78–1.64 (m, 3 H), 1.56–1.41 (m, 5 H), 1.21 (dd, *J* = 13.1, 9.3, 1 H), 1.14 (s, 3 H), 1.05 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR δ 158.96 (s), 104.96 (t), 69.06 (d), 53.33 (s), 52.27 (d), 47.89 (t), 45.99 (d), 42.32 (s), 41.66, 40.55 (2 t), 31.80 (q), 31.51 (t), 30.80 (q), 29.04 (t), 26.04 (q).

(+)-$\Delta^{8(9)}$-Capnellene ((+)-37). Chromatography of (+)-**12** on activated SiO_2 (Aldrich, silica catalyst support, grade 951, pentanes) gave 56% of (+)-**37**. The spectroscopic data are identical with those reported for racemic material;[13c,d] $[\alpha]^{22}_D$ −44.2° (*c* 0.73, $CHCl_3$); IR 3036, 2933, 2863, 1651 w, 1457, 1376, 1364, 792 cm^{-1}; ^1H NMR δ 5.12–5.11 (m, 1 H), 2.79–2.77 (m, 1 H), 2.69–2.63 (m, 1 H), 2.48–2.40 (m, 1 H), 2.01–1.94 (m, 1 H), 1.83 (dd, *J* = 13.1, 8.9, 1 H), 1.67–1.65 (m, 3 H), 1.57–1.42 (m, 5 H), 1.28 (dd, *J* = 13.1, 7.6, 1 H), 1.09 (s, 3 h), 1.02 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR δ 143.09 (s), 121.98, 64.42, 65.77 (3 d), 52.70 (s), 50.93 (t), 43.55 (d), 42.21 (s), 41.73, 40.24, 39.29 (3 t), 31.29, 30.65, 25.50, 15.09 (4 q).

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Registry No. (+)-**12**, 123808-89-9; (−)-**12**, 68349-51-9; **13**, 123754-09-6; (+)-**15**, 98203-44-2; (−)-**15**, 123808-97-9; (+)-**16**, 119241-48-4; (+)-**17**, 119146-42-8; (+)-**18**, 119146-43-9; (+)-**19**, 119239-78-0; (+)-**20**, 119146-44-0; 6-epi-**20**, 123808-94-6; **21**, 123754-10-9; 6-epi-**21**, 123808-95-7; **21** carbinolamine, 123775-20-2; (*R*)-**22**, 123754-11-0; (*S*)-**22**, 123754-23-4; (*R*)-**23**, 123754-12-1; (*S*)-**23**, 123754-24-5; (−)-**24**, 123754-13-2; (+)-**25**, 123808-90-2; (+)-**26**, 123754-14-3; (+)-**27**, 123754-15-4; (+)-**28**, 123754-16-5; epi-**28**, 123808-96-8; **29**, 123808-91-3; (+)-**30**, 123754-17-6; (+)-**31**,

123754-18-7; (+)-**32**, 123754-19-8; (+)-**33**, 123754-20-1; (+)-**34**, 123754-21-2; (+)-**35**, 123754-22-3; (+)-**36**, 123808-92-4; (+)-**37**, 123808-93-5; (*S*)-valinol, 2026-48-4; levulinic acid, 123-76-2; (*R*)-valinol, 4276-09-9.

Supplementary Material Available: Experimental details for (*S*)-**23** and all ^{1}H NMR spectra for all intermediates and ^{13}C NMR spectra for capnellenes (30 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Vallesamidine

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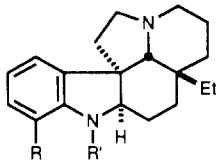
This article reports full details of a project aimed at providing synthetic access to the 2,2,3-trialkylindoline alkaloids such as vallesamidine (**4**). The basic strategy was to preassemble the tricyclic portion containing the nonindolic nitrogen and to form the indoline ring at a late stage in the synthesis. An approach summarized in the retrosynthetic analysis summarized in Scheme III failed because enones **48** and **50** do not undergo 1,4-addition of nitrogen nucleophiles. However, the retrosynthesis summarized in Scheme X did lead to a successful synthesis of (±)-**4**. The synthesis requires seven steps from 2-ethylcyclopentanone [→ **54** → **56** → **66** → **68** → **71** → **74** → (±)-**4**] and delivers the alkaloid in 19% overall yield. Pivotal steps in the synthesis are the lactam annelation process in which **56** reacts with *o*-nitrocinnamic acid to yield **66** and the NBS-mediated cyclization of amino lactam **68** to the pentacyclic bromo lactam **70**. Four of the seven steps involve the formation of skeletal (C–C or C–N) bonds and only three are functional-group transformations.

Much research has been devoted to the synthesis of 2,3,3-trialkylindoline alkaloids, typified by the *Aspidosperma*[3] and *Strychnos*[4] alkaloids aspidospermine (**1**) and strychnine (**3**). Far less attention has been given to 2,2,3-trialkylindoline alkaloids such as vallesamidine (**4**)[5-8] and andrangine (**5**).[9-11] We therefore set out to explore some novel synthetic routes to these types of alkaloids and chose vallesamidine (**4**) as the synthetic target. This report outlines the background information, the retrosynthetic analyses, the results of several synthetic approaches, and the eventual total synthesis of the alkaloid.[12]



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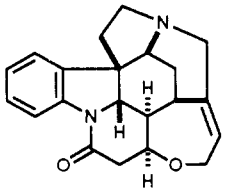
2: R = H, R' = Me



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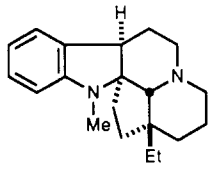

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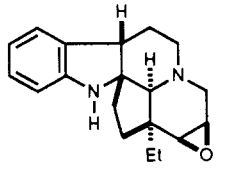
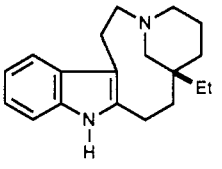


5

Vallesamidine (**4**) was isolated in 1965 from *Vallesia dichotoma* (Ruiz et Pav).[5] On the basis of chemical and physical data, it appeared to be isomeric with *N*-methylaspidospermidine (**2**); however, because of the amount of material available, a definite structure could not be assigned. Djerassi et al.[13] subsequently determined the molecular structure and absolute configuration of vallesamidine by X-ray diffraction. This work, which confirmed speculations by Kutney et al.,[14] was the first determination of the absolute configuration of an alkaloid related to aspidospermine (**1**).

The aspidospermine skeleton can be generated by oxidative cyclization of quebrachamine (**6**).[13,14] Vallesamidine differs from aspidospermine in that C-19 is attached to the indoline ring at C-2 rather than at C-12, suggesting that the biosynthesis of *Aspidosperma* alkaloids involves quebrachamine-type intermediates and that vallesamidine may be regarded as the product of an "abnormal" cyclization, generating the same stereochemistry at carbons 2, 12, and 19 as the "normal" (*Aspidosperma*) cyclizations.[6]



6

Vallesamidine is a structurally unique compound that does not belong to any one particular class of alkaloids. In addition to being related to the *Aspidosperma*[3] alkaloids, it is structurally related to the *Schizozygia* alkaloids (e.g. schizozygine (**7**)).[15-18] The only other compound having the same skeletal system is andrangine (**5**).[10] The absolute configurations of vallesamidine and andrangine

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