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Total Synthesis of (±)- and (−)-Ptilocaulin

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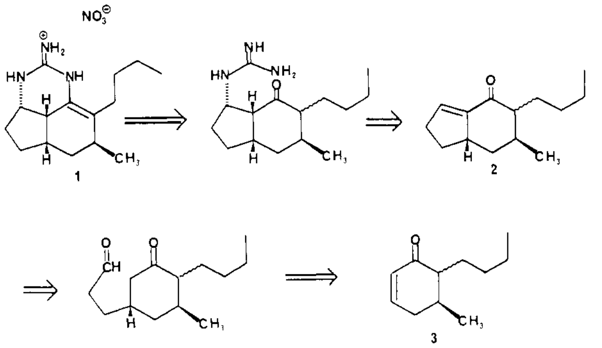
Abstract: An efficient five-step synthesis of (±)-ptilocaulin (**1**) is described. The key step is the addition of guanidine to enone **2** to give **1**. An analogous five-step synthesis of (−)-ptilocaulin (**16**) from (*R*)-5-methyl-2-cyclohexenone (**11**) establishes the absolute stereochemistry of natural (+)-ptilocaulin as **1**.

Rinehart et al. have recently reported the isolation of the antimicrobial and cytotoxic cyclic guanidine (+)-ptilocaulin (**1**) from the Caribbean sponge *Ptilocaulis* aff. *P. spiculifer*.[2] The structure of **1** was assigned on the basis of spectroscopic data and an X-ray crystal structure. The absolute stereochemistry of **1** was not determined. It was suggested that this novel toxin was "derived from addition of guanidine to a polyketonide chain".[2]



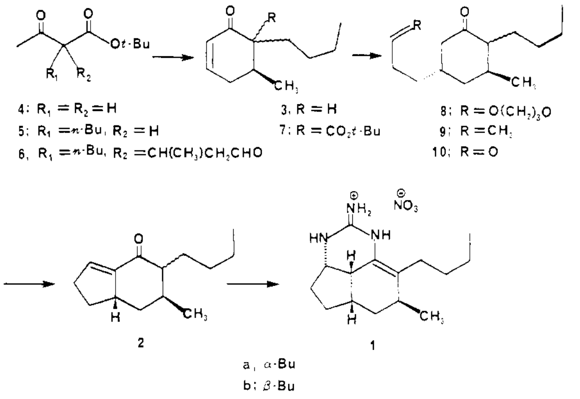
The novel structure of **1** and its potent biological activity make this a significant synthetic target. We have previously reported in a preliminary account an efficient synthesis of (±)-ptilocaulin.[3] We report here the details of that synthesis in improved form and a synthesis of (−)-ptilocaulin of known stereochemistry which establishes the absolute stereochemistry of natural (+)-ptilocaulin as **1**.

Results and Discussion

Our retrosynthetic analysis is based on the Michael addition of guanidine to enone **2** to give a β-guanidino ketone which should undergo intramolecular enamine formation to give ptilocaulin. Related additions of guanidine to enones are well-known, although dihydropyrimidines with an endocyclic double bond are the normal product.[4] In addition, the conversion of **2** to **1** requires that the Michael addition occur from the apparently more hindered α face. The brevity of this scheme warranted the exploration of this route based on a high-risk step.

Enone **2** should be readily available by the conjugate addition of a 3-oxopropyl anion equivalent to 6-butyl-5-methyl-2-cyclohexenone (**3**) followed by an aldol condensation.[5] The stereochemistry of the methyl group and ring-fusion hydrogen of **2** should be established stereospecifically since conjugate addition to 5-substituted cyclohexeneones leads to *trans*-3,5-disubstituted cyclohexanones.[6]

Synthesis of (±)-Ptilocaulin. The preparation of **3** was accomplished by a modification of the procedure of Carney and Johnson for the synthesis of 6-(butyn-3yl)-2-cyclohexenone.[7] *tert*-Butyl acetoacetate (**4**) was converted to **5** in 55% yield (Na, *n*-BuI, dioxane).[8] Sodium methoxide catalyzed conjugate addition of **5** to crotonaldehyde in methanol at −40 to 0 °C gave a 19% yield of **6** (39% based on recovered **5**). Aldol condensation, hydrolysis, and decarboxylation were accomplished by stirring **6** in 100:10:1 acetic acid–concentrated hydrochloric acid–water to give a 58% yield of an ~1.7:1 mixture of **3a** and **3b**. The stereochemistry was assigned on the basis of the characteristic shielding of the methyl protons (δ 0.92 vs. 1.07) and carbon (δ 14.7 vs. 19.1) in the minor cis isomer, **3b**. The yield was improved by carrying out the conjugate addition of **5** to crotonaldehyde at 25 °C. At this temperature aldol reaction also occurred to give **7** which was hydrolyzed and decarboxylated as above to give a 46% yield, from **5**, of a 2:1 mixture of **3a** and **3b**.



Cyclohexenone **3** was converted to indenone **2** by a modification of the procedure of Bal, Marfat, and Helquist.[5] Treatment of **3** with the cuprate prepared from 2-(1,3-dioxan-2-yl)ethylmagnesium bromide[9] and a cuprous bromide–dimethyl sulfide complex gave a 63% yield of **8** as an ~2:1 inseparable mixture of isomers as determined by ^{13}C NMR analysis. Treatment of **8** with hydrochloric acid in DME gives a 63% yield of **2** as an ~1:1 mixture of easily separable isomers. The stereochemistry of **2a** and **2b** was assigned analogously to that of **3a** and **3b**.

The cuprate addition of **3** apparently occurs stereospecifically trans to the 5-methyl group regardless of the stereochemistry of the butyl group. Cuprate additions to 5-alkylcyclohexenones are known to give *trans*-3,5-dialkylcyclohexanones.[6] The addition to **3b** could therefore be predicted a priori to give only **8b**. The stereochemistry of the addition to **3a** was less clear a priori, but apparently **3a** gives **8a** stereospecifically.

The stereochemistry of the cuprate addition was more clearly defined by addition of the cuprate[10] prepared from 3-butenyl-

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[1] Fellow of the Alfred P. Sloan Foundation 1979–1983. Camille and Henry Dreyfus Treacher-Scholar 1982–1987.

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magnesium bromide and cuprous bromide–dimethyl sulfide complex to **3** which gave a 45% yield of a chromatographically separable 1.7:1 mixture of **9a** and **9b** as the only two isomers observed. Ozonolysis of this mixture gave a quantitative yield of **10** which was cyclized with HCl in THF to a 1:1 mixture of **2a** and **2b** in 70% yield. Alternatively, ozonolysis of either pure **9a** or **9b** and acid catalyzed cyclization gave **2** as a 1:1 mixture of isomers. This established that **9a** and **9b** are isomeric at the butyl group and that separation of the isomers of **3** or **8** is not useful since epimerization occurs on cyclization to give **2**.

Treatment of **2a**, **2b**, or the mixture of isomers with guanidine in benzene at reflux under nitrogen with azeotropic removal of water followed by addition of a slight excess of dilute nitric acid gave (±)-ptilocaulin nitrate, mp 165–166.5 °C, in 35–40% yield after chromatography. Only trace amounts of other cyclic guanidinium compounds were isolated. Synthetic (±)-**1** is identical with the natural material by IR, ^{1}H and ^{13}C NMR, mass spectral, and TLC comparison.[11]

The selective formation of ptilocaulin from **2** under mild conditions lends credence to the proposal[2] that ptilocaulin arises "from addition of guanidine to a polyketonide chain". The selectivity would not be surprising if ptilocaulin is the thermodynamically stable isomer. The Michael addition could be reversible with the reaction driven by enamine formation. The stereochemistry of the ring fusion and position of the double bond could be established by equilibration.

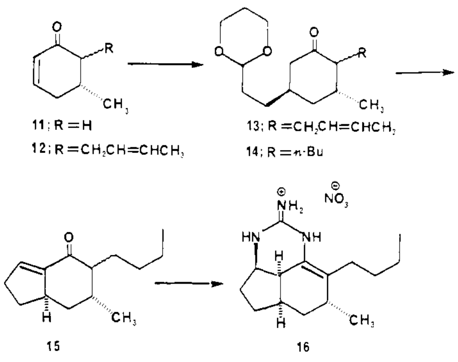
This synthesis leads efficiently to (±)-ptilocaulin in only five steps. The key step, addition of guanidine to **2**, which selectively introduces two of the four stereocenters of ptilocaulin, may be related to its biosynthesis. This reaction should also be useful for the straightforward synthesis of a variety of analogues for pharmacological testing.

Synthesis of (−)-Ptilocaulin. The absolute stereochemistry of ptilocaulin was not established during the structure determination. We therefore chose to adapt the above synthesis to the preparation of optically active ptilocaulin of known stereochemistry. Attempted alkylation of the nonconjugated kinetic enolate[12] of (*R*)-(+)-5-methylcyclohexenone[13] (**11**) with *n*-butyl iodide was unsuccessful. However, this enolate, prepared from **11** with LDA in THF, did react with crotyl bromide in the presence of HMPA to give a 66% yield of an ~4:1 mixture of **12a** and **12b**. Conjugate addition of the cuprate reagent prepared from 2-(1,3-dioxan-2-yl)ethylmagnesium bromide as described above for the conversion of **3** to **8** gave a 61% yield of a 4:1 mixture of **13a** and **13b**. Hydrogenation of this mixture in ethanol over Pd gave a quantitative yield of an ~4:1 mixture of **14a** and **14b**. Acid-catalyzed hydrolysis and cyclization as described in the racemic series gave 24% of (−)-**15b** and 33% of (+)-**15a**. Reaction of (+)-**15a** with guanidine as previously described gave (−)-ptilocaulin nitrate (**16**), mp 181–182 °C, identical with the natural product in all respects except for the $[\alpha]_D$ and CD spectra which are of comparable magnitude but opposite sign. This establishes that natural (+)-ptilocaulin has the absolute stereochemistry shown in **1**.

Experimental Section

NMR spectra were recorded on Varian EM390, Perkin-Elmer R32, Bruker WH-90 (^{13}C NMR), and homemade 270-MHz spectrometers. CD spectra were measured on a JOBIN-YVON Auto. Dichrograph Mark V Spectrometer. Optical rotations were measured on a Hilger-Watts Polarimeter. GC analyses were carried out on $^1/_4$ in. × 10 ft 10% Carbowax 20M on 60/80 Chromosorb WNAW(A) and $^1/_4$ in. × 10 ft 3% SE-30 on 70/80 Chromosorb G(B) columns. Analyses were performed by Galbraith Laboratories.

Guanidine (90%) was purchased from Fluka Chemical Corp. Magnesium was purchased from Reade Manufacturing Co. Inc. (*R*)-(+)-3-Methylcyclohexanone, $[\alpha]^{24}{}_D$ +13.5° (neat), was purchased from Aldrich Chemical Co. and converted to **11**, $[\alpha]^{25}{}_D$ −83° (*c* 1.86, $CHCl_3$), by the literature procedure.[13] THF was distilled from sodium–benzophenone–ketyl.



a, β-R
b; α-R

***tert*-Butyl Butylacetoacetate (5).** With use of the method of Renfrow and Renfrow,[8] *tert*-butyl acetoacetate (**4**) (34.80 g, 0.22 mol) in dioxane (120 mL) was treated sequentially with sodium metal (4.60 g, 0.20 mol) and *n*-butyl iodide (40.48 g, 0.22 mol) to produce 23.44 g (55%) of **5**; bp 83–87 °C (3 torr) [lit.[8] bp 110 °C (10 torr)].

6-Butyl-5-methyl-2-cyclohexenone (3). To a solution of **5** (4.0 g, 18.7 mmol) in MeOH (20 mL) was added sodium methoxide (0.013 g, 0.58 mmol) in MeOH (0.67 mL) at room temperature with stirring. Crotonaldehyde (1.31 g, 18.7 mmol) was added dropwise over 15 min at 0 °C. After the addition was complete, the solution was warmed to room temperature and stirred for 23 h. The reaction was quenched by addition of 0.87 mmol of acetic acid in 1.0 mL of ether. The mixture was poured into 5% $NaHCO_3$ solution (30 mL) which was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to produce 5.22 g of a yellow oil, predominantly **7**, which was dissolved in acetic acid (40 mL), H_2O (0.4 mL), and concentrated HCl (4 mL). The reaction mixture was stirred at 25 °C under a stream of N_2 for 19 h. The solvent was evaporated and the residue was dissolved in $CHCl_3$ (50 mL). The organic layer was washed with 5% $NaHCO_3$ (2 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and evaporated to produce 2.88 g (93%) of crude **3**. Short-path distillation in the presence of hydroquinone gave 1.428 g (46%) of **3** as a colorless oil; bp 83–87 °C (0.6 torr). The enone **3** was shown by GC and ^{13}C NMR to consist of 63% of **3a** and 37% of **3b**. The spectral data for the mixture follow: NMR ($CDCl_3$) δ 6.81 (m, 1), 5.95 (br d, 1, J = 9.9 Hz), 1.12–2.69 (m, 10), 1.07 (d, 3, J = 6 Hz, **3a**), 0.92 (d, 3, J = 6 Hz, **3b**), 0.90 (t, 3, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ (**3a**) 200.7, 146.8, 128.3, 52.9, 32.1, 31.9, 28.0, 26.9, 22.4, 19.1, 13.4; NMR ($CDCl_3$) δ (**3b**) 201.4, 146.6, 128.2, 51.2, 32.0, 29.0, 24.1, 22.2, 14.7, 13.4, one resonance was obscured; IR (neat) 3037, 1679, 1391 cm^{-1}; GC (A, 150 °C) t_R = 21.7 (**3a**) and 23.3 (**3b**) min. An analytical sample was obtained by preparative GC. Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found C, 79.70; H, 10.85.

2-Butyl-5-(2-(1,3-dioxan-2-yl)ethyl)-3-methylcyclohexanone (8) was prepared by using a modification of the procedure of Bal, Marfat, and Helquist.[5] Magnesium turnings (0.49 g, 20.2 mmol) were ground with a mortar and pestle under a N_2 atmosphere and transferred to a flask which was subsequently flame-dried. A solution of 2-(2-bromoethyl)-1,3-dioxane[9] (1.41 g, 7.2 mmol) and 1,2-dibromoethane (0.054 g, 0.3 mmol) in THF (1.3 mL) was added at 25 °C. Upon stirring, the reaction mixture heated up and was periodically cooled with a water bath. After 15 min the mixture had solidified and more THF (0.5 mL) was added. After a total of ~2 h, the suspension was diluted with THF (3.5 mL) and transferred via cannula to a stirred solution of $CuBr\cdot(CH_3)_2S$ (0.74 g, 3.62 mmol) in $(CH_3)_2S$ (6.7 mL) at −78 °C. The resulting orange-red solution was stirred at −78 °C for 1 h. Enone **3** (0.37 g, 2.2 mmol) in Et_2O (6.8 mL) was added dropwise over 3.5 h. The mixture was slowly warmed from −78 to −10 °C over a 14-h period and then stirred at 0 °C for 3 h. Quenching of the reaction was accomplished by pouring the mixture into a solution made up of saturated aqueous NH_4Cl (40 mL) and NH_4OH (10 mL) and stirring at 25 °C for 1 h. Ether was added and the layers were separated. The aqueous layer was extracted with additional Et_2O (2 × 35 mL) and the combined organic layers were washed with H_2O (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and evaporated to produce 0.879 g of crude **8**. Chromatography on silica gel (6:4 hexane–ether) gave 0.398 g (63%) of **8** as a 2:1 mixture of products which were isomeric at the carbon bearing the butyl group. The spectral data for the mixture follow: NMR ($CDCl_3$) δ 4.50 (t, 1, J = 5 Hz),

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3.58–4.27 (m, 4), 1.06–2.60 (m, 19), 0.97 (d, 3, *J* = 7 Hz, **8a**), 0.75 (d, 3, *J* = 7 Hz, **8b**), 0.87 (t, 3, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ (**8a**) 214.1, 102.0, 66.7 (2 carbons), 57.1, 45.2; ^{13}C NMR ($CDCl_3$) δ (**8b**) 212.4, 102.0, 66.7 (2 carbons), 54.1, 48.5; the following peaks could not be assigned—39.2, 34.7, 34.3, 32.5, 30.9, 29.7, 25.9, 25.8, 22.8, 22.6, 20.3, 13.8; IR (neat) 1709, 1148 cm^{-1}; GC (B, 200 °C) t_R = 35.9 (**8a**) and 40.0 (**8b**) min. An analytical sample was obtained by evaporative distillation (135 °C, 0.5 torr). Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.38; H, 10.89.

5-Butyl-1,2,5,6,7,7a-hexahydro-6-methyl-4*H*-inden-4-one (2). A solution of 0.215 g (0.76 mmol) of **8** in 10.3 mL of DME was treated with 1.06 mL of 5 N HCl. The mixture was stirred at 45 °C for 7 h, diluted with Et_2O (25 mL), and quenched with a 5% $NaHCO_3$ solution (25 mL). The layers were separated and the organic layer was washed with brine (25 mL), dried ($MgSO_4$), and evaporated to produce 0.169 g of crude **2**. Chromatography on silica gel (95:5 hexane–ether) gave 0.032 g (20.4%) of **2b** followed by 0.036 g (23.0%) of **2a**. An additional 0.0302 g of material was obtained as a mixture of the two isomers for a total yield of 0.0985 g (63%) of **2**.

The spectral data for **2b** follow: NMR ($CDCl_3$) δ 6.42 (m, 1), 3.08 (m, 1), 1.10–2.55 (m, 14), 0.88 (d, 3, *J* = 7.6 Hz), 0.88 (t, 3, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 202.2, 145.5, 135.6, 54.6, 41.5, 39.3, 33.7, 33.5, 32.0, 29.6, 25.6, 22.8, 14.1, 14.0; IR (neat) 2953, 2928, 2856, 1684, 1618, 1455 cm^{-1}; GC (A, 190 °C) t_R = 20.6 min.

The spectral data for **2a** follow: NMR ($CDCl_3$) δ 6.54 (m, 1), 3.05 (m, 1), 1.13–2.73 (m, 14), 1.04 (d, 3, *J* = 7.6 Hz), 0.86 (t, 3, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 203.2, 143.6, 137.2, 55.2, 40.2, 33.4, 33.2, 32.9, 31.4 (2 carbons), 29.0, 22.0, 19.6, 13.4; IR (neat) 2955, 2930, 2852, 1683, 1616, 1267 cm^{-1}; GC (A, 190 °C) t_R = 17.7 min.

An analytical sample of **2** was obtained by preparative GC. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.46; H, 10.83.

(±)-Ptilocaulin (1). A 0.69 M solution of guanidine (90%, Fluka) in MeOH was prepared and a 0.35-mL aliquot was transferred to a flask fitted with a Dean Stark trap and septum. After removal of the excess solvent under reduced pressure, the flask was charged with N_2 and **2a** (0.032 g, 0.156 mmol) in dry benzene (20 mL) was added by syringe. The reaction mixture was heated to reflux, with stirring, under a N_2 atmosphere. The success of the reaction is dependent upon the rigourous exclusion of air, for the unprotonated form of the product is readily oxidized. When the theoretical volume of water had been collected (25 h), the reaction was allowed to cool and then quenched with 1% nitric acid (2.2 mL, 0.240 mmol). The layers were separated and the aqueous layer extracted with $CHCl_3$ (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to produce 0.072 g of crude (±)-ptilocaulin nitrate. Chromatography on silica gel (83:17) $CHCl_3$–MeOH) gave 0.018 g (37%) of pure ptilocaulin nitrate, mp 158–161 °C. Recrystallization from EtOH–ether gave white crystals: mp 165–166.5 °C; NMR ($CDCl_3$, 270 MHz) δ 8.97 (br, 1), 8.28 (br, 1), 7.44 (br, 2), 3.73 (m, 1), 2.43 (m, 4), 2.11 (m, 2), 1.72 (m, 2), 1.52 (m, ≈3), 1.36 (m, ≈4), 1.10 (d, 3, *J* = 6.7 Hz), 0.95 (t, 3, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 152.0, 127.4, 121.3, 53.6, 36.6, 34.1, 32.2, 31.7, 29.8, 29.7, 28.2, 25.0, 22.5, 19.5, 13.9; IR (KBr) 3220 (br), 2940, 2910, 2855, 1655, 1596, 1371 cm^{-1}; MS (EI) *m/e* (relative intensity %) 247 (M^+, 31), 232 (66), 204 (83), 189 (89), 174 (100). These data correspond very closely to those reported for ptilocaulin nitrate.[11] The synthetic ptilocaulin nitrate was identical with the natural product by TLC comparison.

Reaction of **2b** with guanidine proceeds in a similar fashion. Treatment of **2b** (0.047 g, 0.228 mmol) with guanidine (0.016 g, 0.251 mmol) in dry benzene yields 0.024 g (34%) of pure (±)-ptilocaulin nitrate after workup and chromatography.

(5*R*)-6-(Buten-2-yl)-5-methyl-2-cyclohexenone (12). A stirred solution of diisopropylamine (0.218 g, 2.2 mmol) in dry THF (4.4 mL) at −78 °C was treated with a 2.6 M solution of *n*-BuLi in hexane (0.83 mL, 2.2 mmol). The solution was stirred 40 min and (*R*)-**11**[13] (0.215 g, 1.96 mmol) in 3.2 mL of THF was added dropwise over 90 min. The resulting mixture was stirred for 30 min at −78 °C and treated with HMPA (0.386 g, 2.15 mmol) and crotyl bromide (80%, 0.727 g, 4.3 mmol). The solution was stirred for 15 min at −78 °C and for 6 h at 0 °C. The reaction was diluted with ether (25 mL) and quenched with water. The layers were separated and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give 0.570 g of crude **12**. Chromatography on silica gel (95:5 hexane–ether) gave 0.033 g (7.8%) of dialkylated material, followed by (0.212 g, 66%) a 4:1 mixture of **12a** and **12b** as determined by NMR and GC analysis: $[\alpha]^{25}_{D}$ −62.3° (*c* 4.48, $CHCl_3$); NMR ($CDCl_3$) δ 6.87 (m, 1), 6.00 (br d, 1, *J* = 11 Hz), 5.45 (m, 2), 1.92–2.77 (m, 6), 1.65 (dd, 3, *J* = 6, 1 Hz), 1.05 (d, 3, *J* = 6 Hz, **12a**), 0.94 (d, 3, *J* = 5.6 Hz, **12b**); ^{13}C NMR ($CDCl_3$) δ (**12a**) 200.3, 147.6, 128.7, 126.7, 124.8, 53.0, 32.4, 31.7, 30.0, 19.1, 17.5; ^{13}C ($CDCl_3$) δ (**12b**) 200.8, 146.6, 128.3, 127.6, 126.2, 51.5 (the remaining peaks could not be assigned); IR (neat) 3045, 1677 cm^{-1}; GC (A, 180 °C) t_R = 32.4 (**12a**) and 36.3 (**12b**) min. An analytical sample was prepared by evaporative distillation (100 °C, 2.5 torr). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.30; H, 9.74.

(3*R*)-(Buten-2-yl)-5-(2-(1,3-dioxan-2-yl)ethyl)-3-methylcyclohexanone (13). Enone **12** (0.105 g, 0.64 mmol) was reacted with the cuprate prepared from the Grignard reagent of 2-(2-bromoethyl)-1,3-dioxane (0.386 g, 2 mmol), $CuBr\cdot(CH_3)_2S$ (0.20 g, 1 mmol), and $(CH_3)_2S$ (1.9 mL) as described above for the preparation of **8**. Normal workup gave 0.264 g of crude **13**. Chromatography on silica gel (6:4 hexane–ether) gave (0.109 g, 61%) a 4:1 mixture of **13a** and **13b**: $[\alpha]^{25}_{D}$ +32.0° (*c* 7.67, $CHCl_3$); NMR ($CDCl_3$) δ 5.42 (m, 2), 4.50 (t, 1, *J* = 5 Hz), 3.93 (m, 4), 1.14–2.61 (m, 15), 1.62 (d, 3, *J* = 5 Hz), 0.99 (d, 3, *J* = 5 Hz, **13a**), 0.75 (d, 3, *J* = 6 Hz, **13b**); ^{13}C NMR ($CDCl_3$) δ (**13a**) 212.3, 126.5, 124.8, 102.1, 66.7 (2 carbons), 57.1, 45.6, 35.4, 34.3, 33.1, 32.6, 32.2, 29.3, 25.8, 20.2, 17.5; ^{13}C NMR ($CDCl_3$) (**13b**) 212.3, 127.5, 126.1, 102.1, 66.7 (2 carbons), 54.4, 48.4, 39.3, 35.7, 34.7, 33.4, 32.4, 31.0, 26.5, 20.4, 13.8; IR (neat) 3020, 1708, 1147 cm^{-1}; GC (B, 200 °C) t_R = 46.9 (**13a**) and 50.4 (**13b**) min. An analytical sample was prepared by evaporative distillation (135 °C, 2 torr). Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.67; H, 10.30.

(3*R*)-2-Butyl-5-(2-(1,3-dioxan-2-yl)ethyl)-3-methylcyclohexenone (14). A solution of **13** (0.065 g, 0.23 mmol) and 5% Pd on carbon (19 mg) in ethanol was hydrogenated in a Parr shaker at 50 PSI for 24 h. The reaction mixture was filtered through Celite and evaporated to give 0.065 g (99%) of crude **14**. Evaporative distillation (125 °C, 1.5 torr) gave 0.64 g (99%) of a 4:1 mixture of **14a** and **14b**: $[\alpha]^{25}_{D}$ +25.7° (*c* 2.99, $CHCl_3$). The spectral data are identical with those of **8a** and **8b**.

(6*R*,7a*R*)-5-Butyl-1,2,5,6,7,7a-hexahydro-6-methyl-4*H*-inden-4-one (15). Cyclization of **14** (0.056 g) in 2.7 mL of DME containing 0.28 mL of hydrochloric acid, as described above for the preparation of **2**, gave 0.045 g of crude **15**. Chromatography on silica gel (95:5 hexane–ether) gave 0.010 g (24%) of **15b**, $[\alpha]^{25}_{D}$ −33.3° (*c* 0.54, $CHCl_3$), followed by 0.014 g (33%) of **15a**, $[\alpha]^{25}_{D}$ +28.9° (*c* 0.75, $CHCl_3$). The spectral data of **15a** and **15b** are identical with those of **2a** and **2b**.

(−)-Ptilocaulin (16). A mixture of **15a** (0.015 g, 0.073 mmol) and guanidine (0.007 g, 0.114 mmol) was converted to (−)-ptilocaulin nitrate as described above in the racemic series. Chromatography on silica gel (83:17 chloroform–methanol) gave 9 mg (40%) of (−)-ptilocaulin nitrate (**16**): mp 181–182 °C [lit.[2] mp 183–185 °C]; $[\alpha]^{25}_{D}$ −71.5° (*c* 0.13, CH_3OH) [lit.[11] $[\alpha]^{23}_{D}$ +74.4° (99.5% CH_3OH)]; CD[θ] = −6100° (227 nm) [natural ptilocaulin[11]]: CD[θ] = +5600° (227 nm). The spectral data are identical with those of synthetic racemic ptilocaulin.

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Registry No. (±)-**1**, 86594-30-1; (+)-**1**·HNO_3, 88586-90-7; (±)-**2a**, 88525-26-2; (±)-**2b**, 88586-84-9; (±)-**3a**, 86509-56-0; (±)-**3b**, 86509-55-9; **4**, 1694-31-1; (±)-**5**, 86509-53-7; (±)-*cis*-**7**, 88525-27-3; (±)-*trans*-**7**, 88525-33-1; (±)-**8a**, 88525-28-4; (±)-**8b**, 88525-29-5; (*R*)-**11**, 54307-74-3; **12a**, 88525-30-8; **12b**, 88586-85-0; **13a**, 88525-31-9; **13b**, 88525-32-0; **14a**, 88586-86-1; **14b**, 88586-87-2; **15a**, 88586-88-3; **15b**, 88586-89-4; (−)-**16**·HNO_3, 88195-34-0; crotonaldehyde, 4170-30-3; 2-(2-bromoethyl)-1,3-dioxane, 33884-43-4; guanidine, 113-00-8; crotyl bromide, 4784-77-4.