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A Short Access to (+)-Ptilocaulin

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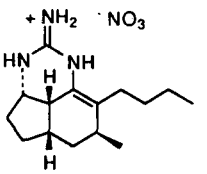
Abstract: A short access to (+)-ptilocaulin involving a photoreductive cyclopropane ring opening of an optically active bicyclo[4.1.0]heptanone derivative is described.

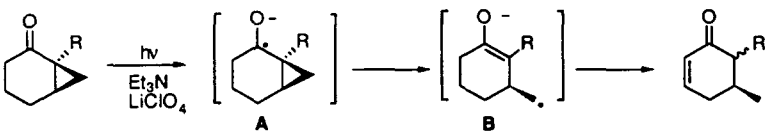
(+)-Ptilocaulin [(+)-**1**] was isolated as a nitrate salt from the orange Caribbean sponge *Ptilocaulis aff. P. spiculifer* in 1981 [1]. This natural product displays antimicrobial activity against Gram-positive and Gram-negative bacteria and significant cytotoxicity towards L 1210 leukemia cells [1].



(+)-Ptilocaulin

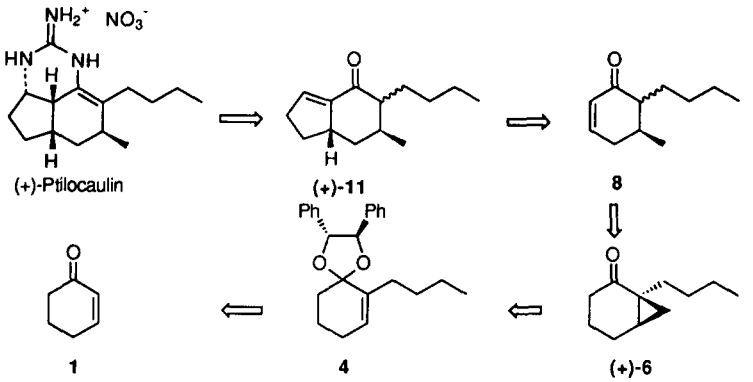
The first total synthesis of racemic (±)-ptilocaulin based on the addition of guanidine was described in 1983 [2]. A second synthesis involving the formation of the six-membered ring by intramolecular [3+2] cycloaddition of a nitrile oxide [3] and a third one relying upon a photochemical 1,3-acyl migration of 1-butyl-*exo*-8-methyl[3.2.2]non-6-en-2-one [4] were reported subsequently. The total asymmetric synthesis of (-)-ptilocaulin [5, 6] and of (+)-ptilocaulin [7] have also been reported. They established unambigously the absolute configuration of natural (+)-ptilocaulin.

Recently, we have shown that the photoreduction of alkyl substituted bicyclo[4.1.0]heptanones [8, 9] with triethylamine leads to the corresponding 3-methylcycloalkanones via intermediates **A** and **B** according to the following Scheme.



We have now applied this reaction to the synthesis of (+)-ptilocaulin. Our immediate target was the bicyclic enone (+)-**6** that was planned to be derived from cyclohexenone **1** as suggested in Scheme I.

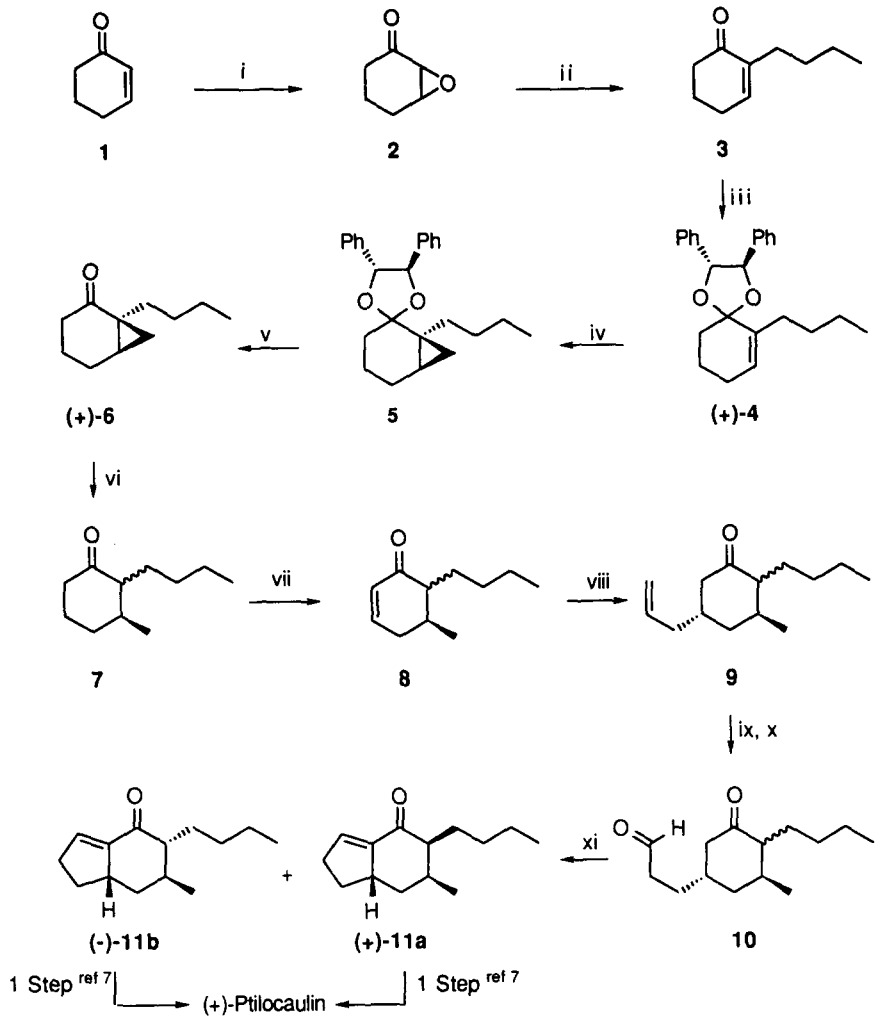
Scheme I: Retrosynthetic analysis of (+)-ptilocaulin



Five steps were required for the elaboration of the bicyclo[4.1.0]heptanone (+)-**6** from cyclohexenone **1** (Scheme II). Epoxidation of **1** (*t*-BuOOH, KF, Al_2O_3) [10] afforded **2** (80 %). The addition of *n*-BuLi (2 eq) to the lithium enolate of **2** (LDA, - 78°C) provided, after acidic work-up (TsOH), the product of SN_2 addition [11] and water elimination **3** in 80 % yield. Treatment of enone **3** with the (R,R)-1,2-diphenylethane-1,2-diol [12] under acidic conditions (PPTS, C_6H_6, heat) afforded the optically pure acetal **4** (yield = 83%; $[\alpha]_D$ = + 82 , *c* = 1.6, $CHCl_3$) which was transformed into the bicyclo[4.1.0]heptanone derivative **5** (95% yield; $[\alpha]_D$ = + 24, *c* = 2.4, $CHCl_3$) through a Simmons-Smith cyclopropanation using CH_2I_2 and $ZnEt_2$ [12] (- 78°C, CH_2Cl_2). The diastereoisomeric excess was 92% as determined by ^1H NMR [13]. Hydrolysis of acetal **5** (HCl 2.7 N in MeOH, 25°C) provided the desired bicyclo[4.1.0]heptanone (+)-**6** isolated in 68 % yield ($[\alpha]_D$ = + 26, *c* = 2, $CHCl_3$, ee = 92% [13]). Irradiation of ketone (+)-**6** in acetonitrile (5 x 10^{-2} M) at 254 nm (quartz vessel) in the presence of triethylamine (10 eq) and $LiClO_4$ (5 eq) [9] led to the desired ketone (+)-**7** (70% yield, $[\alpha]_D$ = + 13, *c* = 2.6, $CHCl_3$, ee = 92% [13]). Its ^1H NMR spectrum revealed the presence of two α-epimers in a 3:1 ratio. The epimerization of (+)-**7** was apparently unavoidable. This mixture of isomers was converted into enone **8** by bromination of its kinetic silyl-enol ether (LDA, TMSCl, -78 °C) followed by debromhydration under basic conditions (Li_2CO_3, LiBr) [14]. Enone **8** was isolated as a 65:35 mixture of two unseparable epimers with a yield of 55%. Treatment of **8** by allyltrimethylsilane in the presence of $TiCl_4$ at -78°C afforded cyclohexanone **9** (2:1 mixture of α-butylketones) [15] with a complete control of the *anti* relative configuration for the alkyl groups at C-3 and C-5 (yield = 92%). Conversion of **9** into the ketoaldehyde **10** started with the chemioselective hydroboration of the alkene moiety using catecholborane in the presence of $Rh(PPh_3)_3Cl$ followed by oxidative work-up with H_2O_2/NaOH [16, 17]. This provided the corresponding alcohol which was transformed into the aldehyde **10** by oxidation with pyridinium chlorochromate. The transformation of **9** to **10** was achieved with an overall yield of 65%. Finally treatment of **10** with aqueous HCl in THF (3.0 N) at 30 °C for 7 hr gave a separable 1:1 mixture of the epimeric α-butylcyclohexanones (+)-**11a** [18] (yield = 35%) and (-)-**11b** [19] (yield = 25%). For these two products, the enantiomeric excess was 92 % as determined by ^1H NMR using Eu(hfc)3 derivative.

Since the conversion of (+)-**11a** and (-)-**11b** into (+)-ptilocaulin (+)-**1** has already been achieved our work realizes a formal synthesis of (+)-ptilocaulin.

Scheme II: Synthesis of (+)-Ptilocaulin



i)KF/Al_2O_3, tBuOOH, 25°C, 80%; ii) a- LDA, -78°C; b- *n*-BuLi -23°C; c- TsOH, 80%; iii) (R,R)-1,2-diphenylethane-1,2-diol, PPTS, 80°C, 83%; iv) $ZnEt_2$, CH_2I_2, CH_2Cl_2, 0°C, 95%; v) HCl (2.7 N)/MeOH, 25°C, 90%; vi) hv, NEt_3 (10 eq), $Li(ClO_4)$ (5eq), CH_3CN, 70%; vii) a- LDA, -78°C, TMSCl; b- Br_2, THF, 0°C; c- Li_2CO_3, LiBr, DMF, 130°C, 55%; viii) $TiCl_4$, allylsilane, -78°C, 92%; ix) a- catecholborane, $Rh(PPh_3)_3Cl$; b- H_2O_2, NaOH, 83%; x) PCC, CH_2Cl_2, 25°C, 83%; xi) HCl/THF (3 N); 30°C; separation by flash chromatography (petroleum ether/AcOEt: 95/5).

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18- Compound **(+)-11a:**
$[\alpha]_D$ = +3 (*c* = 1.6, $CHCl_3$); IR (film): 2856, 1690, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ: 0.84 (t, *J* = 7.5 Hz, 3H); 0.84 (d, *J* = 7.6 Hz, 3H); 1.10-2.45 (m, 14H), 3.06 (m, 1H), 6.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0 (q), 14.2 (q), 22.6 (t), 25.6 (t), 29.6 (t), 33.0 (t), 33.5 (t), 33.8 (t), 39.5 (d), 41.7 (d), 54.5 (d), 134.9 (d), 145.0 (s), 202.0 (s); MS (EI, 70 eV): *m/z* 206 (26), 180 (50), 166 (100), 108 (80).

19- Compound **(-)-11b:**
$[\alpha]_D$ = -65 (*c* = 1.6, $CHCl_3$); IR (film): 2856, 1690, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ: 0.87 (t, *J* = 7.5 Hz, 3H); 1.07 (d, *J* = 7.6 Hz, 3H); 1.15-2.60 (m, 14H), 3.09 (m, 1H), 6.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.0 (q), 19.5 (q), 22.0 (t), 29.2 (t), 31.4 (t), 31.5 (t), 32.8 (t), 33.1 (t), 33.5 (d), 40.1 (d), 55.0 (d), 137.0 (d), 143.5 (s), 203.5 (s) (s); MS (EI, 70 eV): *m/z* 206 (26), 180 (50), 166 (100), 108 (80).

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