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TOTAL SYNTHESIS OF (+)-PTILOCAULIN

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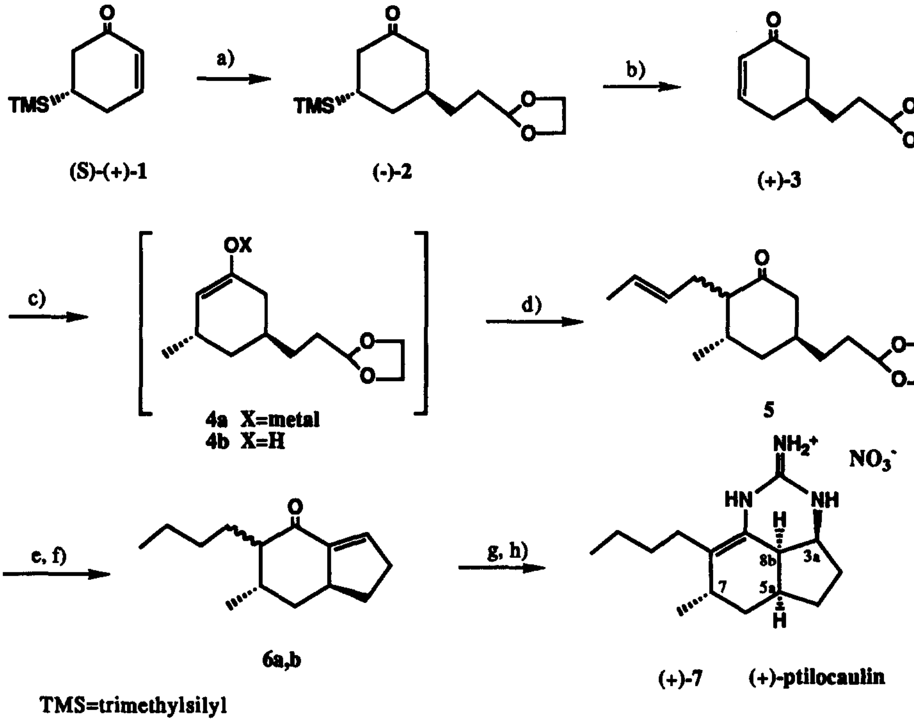
Summary: The first synthesis of (+)-ptilocaulin is described.

(+)-Ptilocaulin was isolated from Caribbean sponge Ptilocaulis aff. P. spiculifer, and it shows antimicrobial and cytotoxic activity.1) Though the absolute stereochemistry has been established by the synthesis of unnatural (-)-enantiomer,2) the synthesis of (+)-ptilocaulin itself has not yet appeared. In this paper we will describe a diastereocontrolled efficient synthesis of (+)-ptilocaulin starting with (S)-(+)-5-trimethylsilyl-2-cyclohexenone (**1**).3)

1,4-Addition of the Grignard reagent prepared from 3-bromo-propanal ethylene acetal to (S)-(+)-**1** gave the trans adduct (-)-**2** [$[\alpha]_D^{23}$-66.1°(c 1.38, $CHCl_3$)] as an exclusive diastereoisomer in 85% yield.4) Elimination of the trimethylsilyl group with $CuCl_2$ (3 equiv) in DMF (55-60 °C, 1 h) gave enone (+)-**3** [$[\alpha]_D^{24.5}$+42.4°0(c 1.87, $CHCl_3$)] in 68% yield.4) 1,4-Addition of dimethylcuprate to (+)-**3** also proceeded in a diastereoselective manner5) (Et_2O, -5 °C, 1 h), and afforded **5**6) in 80% overall yield after alkylation of the intermediary enolate **4a** with crotyl bromide (Et_2O-THF-HMPA=4:1:1, -5 °C, 1.5 h). Hydrogenation of the double bond followed by treatment with 2 M aq. HCl-THF (75-80 °C, 3 h) gave the bicyclic enone **6** as a mixture of two diastereoisomers (1:1) in 80% yield. The diastereoisomers can be separable by flash column chromatography, however, separation of them is not useful since epimerization occurs in the next step. Thus, treatment of the diastereoisomeric mixture with guanidine (1.2-1.5 equiv) according to the method of Snider2) (reflux in benzene for 24 h with removal of water) followed by treatment with dil. nitric acid gave a mixture of (+)-ptilocaulin and its C-3a epimer (ca. 1:1) in 35-42% combined yield as their nitrates.7) Careful column chromatography (silica gel; $CHCl_3$:MeOH=85:15) and recrystallization gave pure (+)-ptilocaulin nitrate8)[mp 182.5-4.0 °C, lit.1) mp 183-5 °C; $[\alpha]_D^{19}$+74.1°(c 0.34, MeOH), lit.2) $[\alpha]_D^{23}$+74.4°(99.5% MeOH)].8)



Scheme 1. a) RMgBr, Me_2S-CuBr; b) $CuCl_2$, DMF; c) Me_2CuLi; d) crotyl-Br; e) H_2, Pd-C; f) H_3O^+; g) guanidine; h) dil. HNO_3.

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4) In general, 1,4-addition of Grignard reagents to **1** proceeds in a highly diastereoselective manner: M. Asaoka, K. Shima, N. Fujii, and H. Takei, Tetrahedron, **44**, 4757 (1988).
5) No diastereoisomer was detected by GLC and ^{13}C NMR for **4b**.
6) A chromatographically inseparable diastereoisomeric mixture at α-carbon of the carbonyl group.
7) The structure of the epimer was assigned by an X-ray analysis.
8) The ^{1}H (270 MHz) and ^{13}C (67.5 MHz) NMR spectra showed good agreement with those of provided by Uyehara.$^{9)}$
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