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A Formal Synthesis of Ptaquilosin
The Aglycon of a Potent Bracken Carcinogen Ptaquiloside

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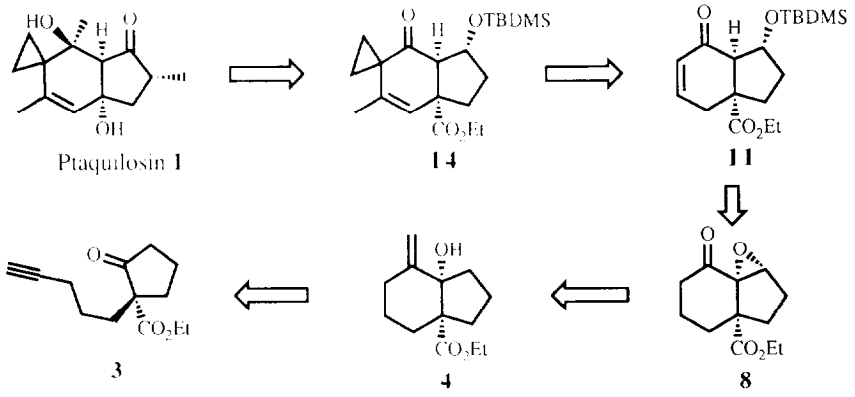
Abstract : A formal synthesis of racemic and optically active ptaquilosin has been achieved from the commercially available methyl 2-oxocyclopentanecarboxylate.

Recently ptaquilosin **1**, the aglycon of the carcinogen ptaquiloside,[2] has been evaluated for its antitumor activity at the NCI and has shown toxicity toward human myelocytic leukemia and other carcinoma cells of various species of origin.[3]

Kigoshi and co-workers reported the synthesis of (+)-ptaquilosin **1** with an overall yield of 2.4%.[4a] On their side, Padwa and co-wokers have proposed a convergent approach that utilizes the dipolar cycloaddition of carbonyl ylide dipole in the key step leading to the construction of the ptaquilosin skeleton.[5]

We would like to report here a new approach to the racemic and optically active ptaquilosin skeleton that features a photoreductive cyclization of unsaturated ketones and a photoreductive ring opening of α,β-epoxyketones leading to the bicyclic compound **11**, which can then be transformed into ptaquilosin **1**.[4]

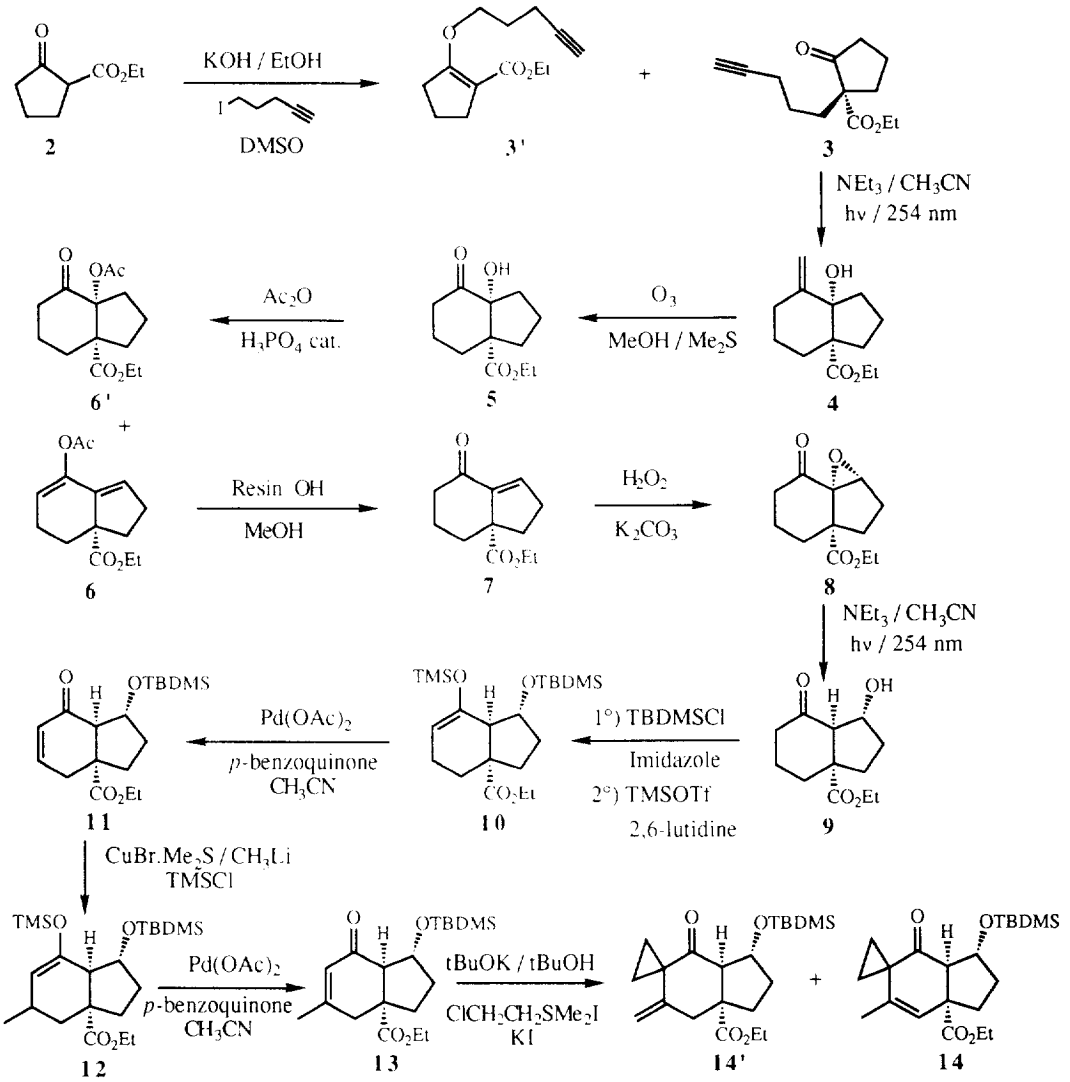
Scheme 1 : Retrosynthesis of Ptaquilosine **1**.



Our plan implies the synthesis of the tricyclic β-hydroxyenone **14** which should be issued from a photoreductive ring opening of the corresponding α,β-epoxyketone **8**. This compound was envisaged to be

derived from the bicyclic hydroxyester **4** which was expected to be obtained through a photoreductive cyclization of the unsaturated β-ketoester **3**.

Scheme 2 : Synthesis of **14**, precursor of (±)-ptaquilosine **1**.



Alkylation of the preformed potassium enolate[6] of the β-ketoester **2** by 5-iodopentyne in DMSO produced the C-alkylated product **3** in 81% yield along with 3-8% of the O-alkylated product **3'**. After purification of **3** by flash chromatography, this compound was irradiated in the presence of triethylamine (5 eq) in acetonitrile ($5x10^{-2}$ M) at 254 nm.[7] The corresponding bicyclic product **4** obtained in 70% yield was submitted to ozonolysis, affording ketone **5** with a yield of 82%.

Treatment of **5** with acetic anhydride in the presence of a catalytic amount of phosphoric acid at 60° C led

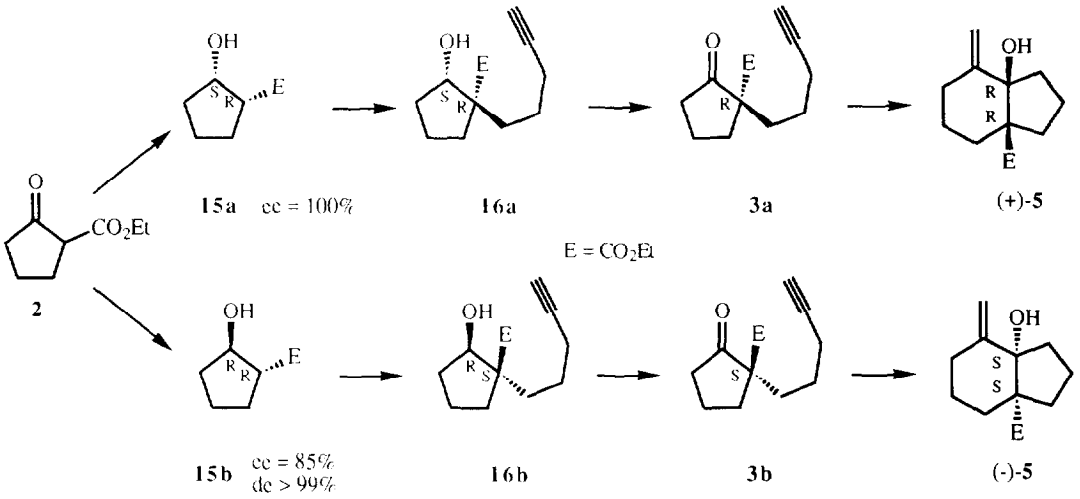
to products **6** (72%) and **6'** (6%) which were separated by flash chromatography. The transformation of **6** to the enone **7** (95% yield) was achieved by treating **6** with Amberlite® IRN-78 $^{\ominus}$OH. Conversion of **7** into the tricyclic α,β-epoxyketone **8** was accomplished in 81% yield by using H_2O_2 in methanolic potassium carbonate solution.[8] Under these conditions only one isomer was formed.[4b]

Irradiation of an acetonitrile solution of **8** ($5x10^{-2}$ M) at 254 nm[9] in the presence of triethylamine (10 eq) afforded the β-hydroxyketone **9** in 79% yield. The latter compound was converted into **11** in 46 % yield through a three step process involving first the silylation of the hydroxy group by using TBDMSCl in the presence of imidazole (82%), secondly the treatment of the ketone by TMSOTf in the presence of 2,6-lutidine, which gave the protected silylenol ether **10** (87% yield), and finally the oxidation of **10** with *p*-benzoquinone in the presence of $Pd(OAc)_2$ (65% yield).[10] Treatment of enone **11** with lithium dimethylcuprate (CH_3Li, $Me_2S.CuBr$) in the presence of TMSCl produced the enol ether **12** which was then treated directly with $Pd(OAc)_2$ in the presence of *p*-benzoquinone[10] to give **13** in 40% overall yield.

The introduction of the spirocyclopropane unit at C-7 in **13** was accomplished with 2-chloroethyldimethylsulfonium iodide[11] and KI under basic conditions (*t*-BuOK , *t*-BuOH , 0° C). Two separable cyclopropylketones **14** (40%) and **14'** (15%) were obtained in a 5 : 2 ratio.

With the purpose to prepare both enantiomers of ptaquilosin **1** we adopted the strategy wherein each of the two enantiomers **3a** and **3b** possessing respectively the (R) and (S) configuration at the quaternary carbon would be prepared stereoselectively from the common racemic ketoester **2**. The enantiomer (-)-**5** would lead to natural (-)-ptaquilosin **1**, while the enantiomer (+)-**5** would afford unnatural (+)-ptaquilosin **1**. Compounds (+)-**5** and (-)-**5** were prepared in four steps from β-ketoester **2** by using a highly stereoselective alkylation of 2-hydroxycycloalkane carboxylic ester.[12]

Scheme 3 : Synthesis of (+)-**5** and (-)-**5**.



The ethyl (1S,2R)-2-hydroxycyclopentane carboxylic ester **15a** was obtained by reduction of the commercially available β-ketoester **2** by using *Mucor racemosus* yeast[13] (ee > 99% ; yield = 100%). Ethyl (1R,2R)-2-hydroxycyclopentane carboxylic ester **15b** was obtained by chiral hydrogenation of the β-ketoester **2**

by using Ruthenium (R)-BINAP catalyst[14] (de > 99% ; ee = 85% ; yield = 82%). The alkylation of ethyl (1S,2R)-2-hydroxycyclopentane carboxylate and of its (1R,2R) diastereoisomer was performed in THF by using 2 equivalents of LDA in the presence of HMPA (4.5 eq) and by quenching the dianion with an excess of 5-iodopentyne. Compounds **16a** (ee > 99%) and **16b** (ee ≈ 82%) were obtained as the unique alkylated products[10] with yields of 55% and 60%, respectively. Swern oxidation[15] of **16a** and **16b** afforded the alkylated β-ketoesters **3a** (ee > 99%) and **3b** (ee ≈ 80%) in 87% and 85%, respectively.

These two ketoesters **3a** and **3b** were then irradiated under the photoreductive conditions to produce the bicyclic compounds (-)-**5** (ee > 99%) and (+)-**5** (ee ≈ 78%) with a yield of 50%. This sequence of reactions achieved a formal total synthesis of natural and unnatural ptaquilosin **1**.

The synthesis of **14**, precursor of the ptaquilosin **1** was obtained from ethyl 2-oxocyclopentane carboxylate **2** in thirteen steps with an overall yield of 2%.

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