Tetrahedron Letters,Vol.30,No.15,pp 1983-1986,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

STEREOCONTROLLED TOTAL SYNTHESIS OF (±)-PTAQUILOSIN, THE AGLYCONE OF PTAQUILOSIDE, A BRACKEN CARCINOGEN

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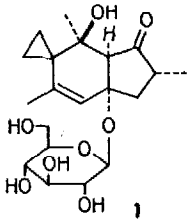
Summary: Starting from α-allyl-δ-valerolactone, stereocontrolled synthesis of ptaquilosin (**2**), the aglycone of a bracken carcinogen ptaquiloside (**1**) has been achieved in racemic form, which includes a novel deformylation-hydroxylation reaction (**21** → **23**) as one of the key steps.

Since bracken fern (Pteridium aquilinum) was shown to be carcinogenic in 1960,[1] intensive studies have been made in search for the carcinogenic principle(s): we isolated a carcinogen ptaquiloside (**1**) from bracken in 1983, elucidated the structure,[2] and proved its potent carcinogenicity.[3] Ptaquiloside (**1**) is transformed under weakly basic or neutral conditions into the active form, dienone **3**,[2a,2d] which causes DNA strand scission base-specifically.[4] Ptaquilosin (**2**), the aglycone of **1** is also converted to dienone **3** under the conditions similar to those for the transformation of **1** into **3**.[5] We describe herein a stereocontrolled total synthesis of racemic ptaquilosin (**2**).



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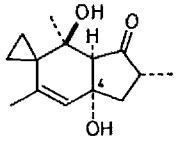

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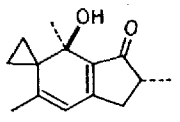

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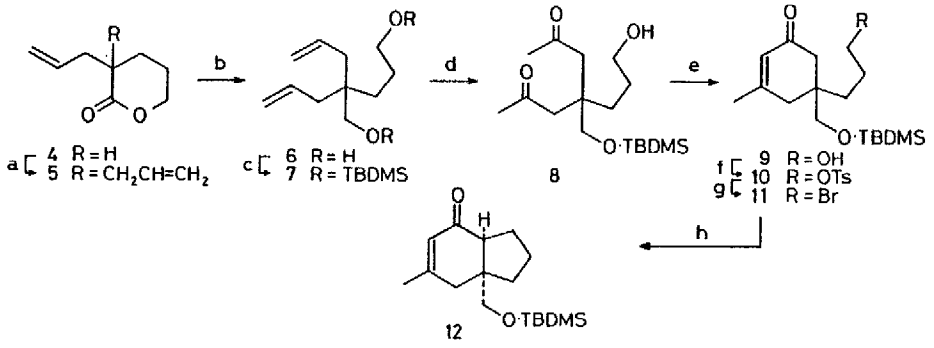
The instability of ptaquilosin (**2**) poses a serious problem for the synthesis program of **2**. The presence of a hydroxyl group at C-4 in **2** is one of the major reasons for the instability of **2**. Thus, we have chosen bicyclic enone **12** as a key intermediate: a siloxymethyl group is converted to a hydroxyl group under mild conditions in the later stage of the synthesis.

The preparation of the key intermediate **12** started with α-allyl-δ-valerolactone (**4**)[6] (Scheme 1). The enolate of **4** was allylated to afford bis-allyl lactone **5**[7] (bp 105-110 °C/2 mmHg, 94%[8]). Reduction of **5** with $LiAlH_4$ followed by silylation of the resulting diol **6** gave disilyl ether **7** (colorless oil, 86% overall). The Wacker-type oxidation of two olefinic bonds in **7** proceeded with concomitant deprotection of one of the two silyl groups providing diketone **8** (colorless oil, 63%).[9] The base-catalyzed intramolecular aldol condensation of **8** led to cyclohexenone **9** (colorless oil, quantitative), which was converted to bromide **11** (colorless oil, 89% overall) via a two-step standard process: (1) tosylation to give tosylate **10** (colorless oil); (2) substitution with LiBr. Intramolecular alkylation of **11** was carried out

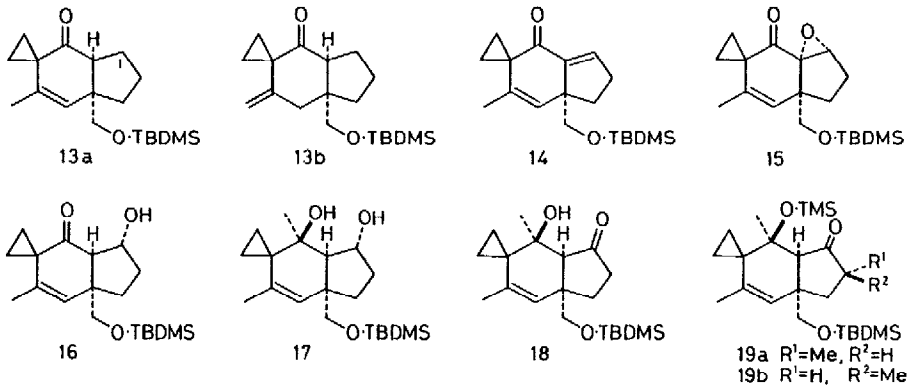
Scheme 1



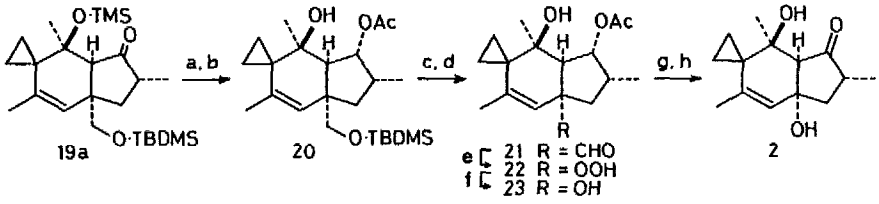
(a) LDA, THF, -75 °C, 1 h then CH_2=$CHCH_2Br$, -50 °C → 5 °C, 4 h; (b) $LiAlH_4$, THF, room temp., 1 h; (c) t-$BuMe_2SiCl$, imidazole, DMF, room temp., 30 min; (d) O_2, $PdCl_2$, CuCl, DMF/H_2O (7:1), 50 °C, 48 h; (e) K_2CO_3, MeOH, 50 °C, 5.5 h; (f) p-TsCl, pyridine, 0 °C, 5 h; (g) LiBr, acetone, reflux, 1 h; (h) LDA (2.0 equiv), HMPA, THF, -78 °C → -35 °C, 2 h.

using LDA to produce bicyclic enone **12** (colorless oil, 90%).[10] The introduction of the spirocyclopropane unit alpha to the keto group in **12** was accomplished with 2-chloroethyldimethylsulfonium iodide[11] and KI under basic conditions (t-BuOK, t-BuOH, room temp., 2.5 h) to afford a separable 4:1 mixture of cyclopropyl ketones, **13a** (mp 39-41 °C, 49%) and **13b** (colorless oil, 12%):[12] **13b** was isomerized to **13a** (93%) on treatment with a catalytic amount of p-TsOH (dioxane, reflux, 1.3 h).

With cyclopropyl ketone **13a** in hand, the stage was set for the task of functionalizing the cyclopentane part. Thus, the hydroxyl group was introduced at C-1 starting with **13a** by the following sequence: (1) phenylselenenylation (LDA, THF, -78 °C, 1 h, then PhSeCl, -78 °C, 1 h) giving a mixture of two diastereomeric phenyl selenides and subsequent elimination (35% H_2O_2, pyridine, CH_2Cl_2, 0 °C, 1 h) to provide conjugated ketone **14** (mp 53-54 °C, 86%); (2) epoxidation (30% H_2O_2, NaOH, MeOH, 10-17 °C, 6 h) leading to α-epoxy ketone **15**[13] (mp 63-64 °C, 86%); (3) reductive cleavage of the epoxy group[14] [Ca, liq. NH_3/THF (1:1), -78 °C, 50 min] to furnish hydroxy ketone **16** (colorless oil, 89%).



Scheme 2



(a) $LiAlH_4$, ether, room temp., 30 min; (b) Ac_2O, pyridine, room temp., 8.5 h; (c) Bu_4NF, THF, room temp., 7 h; (d) CrO_3·pyridine, CH_2Cl_2, room temp., 10 min; (e) O_2, EtOAc, 45 °C, 3.5 h; (f) PPh_3, ether, room temp., 30 min; (g) K_2CO_3, MeOH, room temp., 2 h; (h) PCC, CH_2Cl_2, room temp., 10 min.

Highly stereoselective addition of the Grignard reagent (MeMgI) to **16** took place (ether, room temp., 1 h) to afford desired diol **17** (mp 76-78 °C, 90%).[15,16] Swern oxidation of **17** [DMSO, $(COCl)_2$, CH_2Cl_2, -60 ~ -55 °C, 15 min, then Et_3N, -55 °C, 5 min, -55 °C → room temp., 20 min] yielded ketone **18** (mp 72-73 °C, 99%), which was monomethylated according to the Kuwajima method.[17] Silylation of the dianion of **18** [LDA (13 equiv), Me_3SiCl (15 equiv), DME, 0 °C, 1 h, *then room temp., 50 min*] *gave the enol silyl ether, which was methylated* [$PhCH_2NMe_3$·F (2 equiv), MeI (18 equiv), THF, room temp., 1 h] to provide a separable mixture of diastereomers, **19a** (colorless oil, 28%) and **19b** (colorless oil, 43%): base-promoted *isomerization of* **19b** *to* **19a** (t-BuOK, t-BuOH, 30 °C, 3 h) was achieved (79%). The stereochemistry of the secondary methyl group in two isomers, **19a** and **19b** was determined by converting these two isomers into the conformationally rigid derivatives and by comparing their coupling constants around the secondary methyl groups in the ^1H NMR spectra with those of the appropriate compound derived from natural **1**:[18] thus, the secondary methyl group of the more stable isomer **19a** was proved to possess the correct stereochemistry.

The stage was set to replace the siloxymethyl group in the ring juncture with a hydroxyl group: conditions for the transformation must be *mild enough for the unstable product to* survive. Conversion of **19a** into aldehyde **21** (mp 102-104 °C, 65% overall) was performed by the following sequence (Scheme 2): (1) reductive removal of the trimethylsilyl group in **19a** followed by acetylation to give acetate **20** (colorless oil, 95% overall); (2) desilylation and subsequent Collins oxidation. The concentrated EtOAc solution of **21** was kept under the oxygen atmosphere (45 °C, 3.5 h), and the resulting crude hydroperoxide **22** was reduced with PPh_3 to provide diol **23** (colorless oil, 89% overall).[19] Deacetylation of **23** and oxidation with PCC furnished (±)-ptaquilosin (**2**) (colorless oil, 32% overall), proved to be identical with natural **2**[20] by spectral (IR, ^1H NMR, and mass) and chromatographic comparison.

In summary, (±)-ptaquilosin (**2**), the aglycone of bracken carcinogen (**1**) has been synthesized (1.6% overall yield, 25 steps) *starting with* α-allyl-δ-valerolactone.

Acknowledgments: This work was supported in part by Grant-in-Aid for Special Project Research, Chemical Syntheses for Elucidation of Biological Functions and by Grant-in-Aid for Encouragement of Young Scientists (No. 60740290 and 62740308 to H.K.) from the Ministry of Education, Science, and Culture, Japan.

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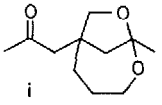
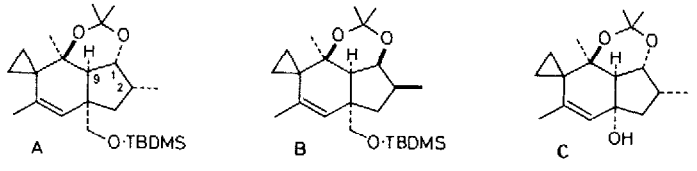
4. M. Ojika, K. Sugimoto, N. Nozaki, T. Okazaki, and K. Yamada, unpublished result.
5. H. Kigoshi, A. Sawada, Y. Imamura, H. Niwa, and K. Yamada, unpublished result.
6. J. L. Herrmann and R. H. Schlessinger, J. Chem. Soc., Chem. Commun., 711 (1973).
7. All new compounds exhibited satisfactory spectroscopic (IR, ^{1}H NMR, and mass) and analytical (microanalysis or exact mass spectra) data.
8. All chemical yields refer to the materials purified by column or preparative layer chromatography on silica gel.
9. Keto acetal **i** was obtained as a byproduct (9%), which resulted from deprotection of two silyl groups during the oxidation of **7**.



i

10. Intramolecular alkylation of tosylate **10** under the same conditions as those employed for the reaction, **11** → **12** produced bicyclic enone **12** in low yield (40%).
11. Cf. S. M. Ruder and R. C. Ronald, Tetrahedron Lett., **25**, 5501 (1984).
12. Spirocyclopropanation of **12** was also effected with $BrCH_2CH_2Br$ under basic conditions ($NaNH_2$, liq. NH_3/THF(10:1), -33 °C, 5 h) to afford a 1:2 mixture of **13a** and **13b** in low yield (34%).
13. A small amount of the diastereomeric β-epoxy ketone was formed (13%).
14. No reductive cleavage of the epoxy group in **15** took place under reduction conditions such as (i) $Cr(OAc)_2$-BuSH; (ii) Zn-NH_4Cl; and (iii) Al(Hg).
15. The diastereomeric diol was obtained in a small amount (2%).
16. In order to confirm the stereostructure of **17** unambiguously, single-crystal X-ray analysis was performed using a triol (mp 146-148 °C) derived from **17** by desilylation (Bu_4NF, THF, room temp., 5 h).
17. (a) I. Kuwajima and E. Nakamura, J. Am. Chem. Soc., **97**, 3257 (1975). (b) I. Kuwajima, E. Nakamura, and M. Shimizu, J. Am. Chem. Soc., **104**, 1025 (1982).
18. The two isomers, **19a** and **19b** were transformed [(1) $LiAlH_4$, ether; (2) CH_2=C(OMe)Me, camphorsulfonic acid, benzene] into isopropylidene derivatives, **A** and **B**, respectively. The compound **C** was prepared from ptaquiloside (**1**) in 8 steps (H. Kigoshi, A. Sawada, H. Niwa, and K. Yamada, unpublished result). The coupling constants in the ^{1}H NMR spectra are as follows: **A**, $J_{1,2} = J_{1,9}$ = 9.6 Hz; **B**, $J_{1,2} = J_{1,9}$ = 4.0 Hz; **C**, $J_{1,2} = J_{1,9}$ = 9.7 Hz.



19. The reaction, **21** → **22** could also be executed under oxygen in a benzene solution containing AIBN (40-60 °C, 8 h) and reduction of **22** with PPh_3 gave **23** (47% overall).
20. The authentic specimen **2** was prepared from natural **1** by chemical transformation: H. Kigoshi, A. Sawada, Y. Imamura, H. Niwa, and K. Yamada, unpublished result.

(Received in Japan 23 January 1989)