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SYNTHESIS OF (-)-[12,12-$^2H_2$]RISHITIN[1)]

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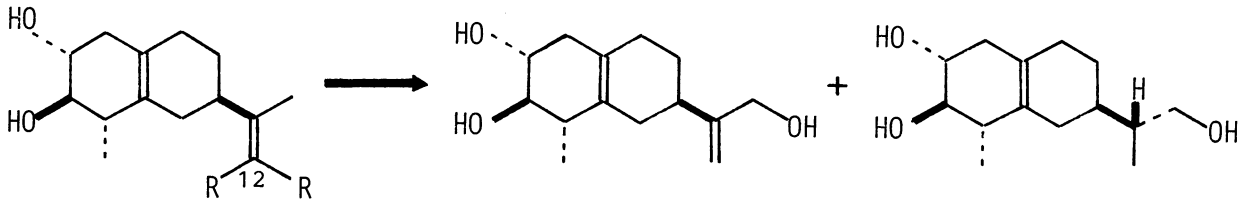
For studies on the vital metabolic pattern of rishitin, a representative phytoalexin of diseased potatoes, (-)-[12,12-$^2H_2$]-rishitin has been synthesized stereoselectively from (11S)-2α-acetoxy-3-oxo-4β,5α-eudesman-6β,12-olide.

In the course of biosynthetic studies on phytoalexins isolated from diseased potatoes, we previously reported that rishitin (1) is metabolized in healthy potato tuber tissues into rishitin M-1 (2) and M-2 (3).[2)] In order to clarify the mutual relationship in the metabolic pathway, we required hot rishitin, labelled with two deuterium atoms at C_{12} position. This communication deals with the synthesis of the title compound, (-)-[12,12-$^2H_2$]rishitin (1a), involving practical improvement of the synthetic pathway for cold rishitin, which has been published by us several years ago.[3)]

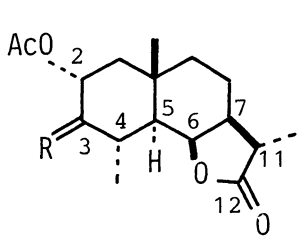


1 R=H 1a R=D 2 3

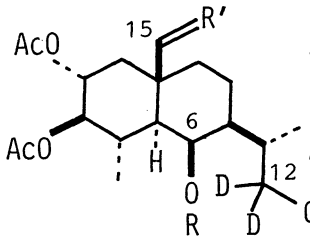
The synthesis was commenced with (11S)-2α-acetoxy-3-oxo-4β,5α-eudesman-6β,12-olide (4),[3)] readily derived from santonin, a totally synthesized sesquiterpene. The compound (4) was treated with the t-butylamine-borane complex[4)] in aqueous methanol (0 °C, 10 min) to give a separable mixture of 3β- and 3α-hydroxy-2-acetates (5 and 6)[3)] in 60 and 38% yields, respectively. The compound (6) could easily be reconverted to the starting material (4) by Jones oxidation in 97% yield. The yield of the desired 3β-hydroxy derivative (5) amounted to 83% by repeated oxidation and reduction of the 3α-ol (6). Incorporation of deuterium into the compound (5) was carried out by treatment with lithium aluminium deuteride (Merck, ^2H-content min 98%) (in THF, reflux, 24 h) followed by acetylation (Ac_2O in Py, 23 °C, 20 h) to afford [12,12-$^2H_2$]-2,3,12-triacetate (7), mp 99-100 °C, in 89% yield, which was converted (NOCl in Py, -20--30 °C, 20 min) quantitatively into the 6β-nitrite (7a). Photolysis of the nitrite (7a) (200-W Hanovia high pressure mercury lamp in C_6H_6, 20 °C, 3.5 h; THF-i-PrOH, reflux, 2.5 h) and subsequent dehydration ($POCl_3$ in Py, 23 °C, 3 d; MsCl in Py, 23 °C, 39 h; collidine, 190 °C , 3 h) were performed under almost the same conditions as those of the cold rishitin

synthesis[3] to give [12,12-$^2H_2$]Δ^5-10-nitrile (8), mp 106-107 °C, in 40% overall yield, via [12,12-$^2H_2$]-15-oxime (9), amorphous. Reductive decyanation[3] of the compound 8 (Na in toluene-EtOH, reflux, 1 h) afforded [12,12-$^2H_2$]$\Delta^{5(10)}$-triol (10), mp 106.5-107 °C in 81% yield.

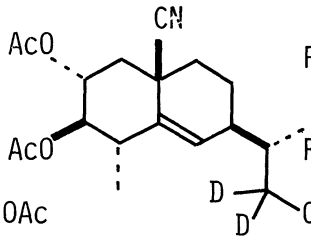
Protection of 2,3-dihydroxyl groups in compound 10 was improved as follows.[5] Tritylation of 10 [$(C_6H_5)_3CCl$, Et_3N and DMAP in DMF, 23 °C, 4 d][6] afforded its 12-monotriphenylmethyl ether (10a), oil, in 91% yield. The compound (10a) was acetylated (Ac_2O in Py, 20 °C, 24 h) and then hydrolyzed with acid (a catalytic amount of TsOH in MeOH, 23 °C, 3 h) to give [12,12-$^2H_2$]-2,3-diacetoxy-12-ol (10b), oil, in 96% overall yield. Successive treatment of 10b (TsCl in Py, 23 °C, 26 h; NaI in acetone, 80 °C, 24 h; 5% KOH in MeOH, reflux, 2 h) provided 1a, oil, in 66% overall yield: $[\alpha]_D^{26}$ = -30.6° (c 2.1, EtOH), (lit.,[7] -35.1° for natural rishitin). (-)-[12,12-$^2H_2$]Rishitin thus obtained was identical with cold rishitin in respects of R_f-values on TLC and ^{1}H-NMR spectra except two protons at C_{12}. The ^{1}H-NMR (400 MHz) and EI-MS spectra[8] of 1a showed that the $^2H_2$ content of the synthetic rishitin (1a) amounted to more than 99.4%.



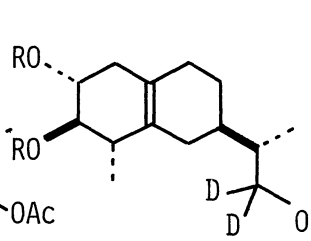
4 R=O
5 R=▬OH, ···H
6 R=···OH, ▬H



7 R=H, R′=H_2
7a R=NO, R′=H_2
9 R=H, R′=NOH



8



10 R=R′=H
10a R=H, R′=CPh_3
10b R=Ac, R′=H

References

1) Part IL of "Studies on the Phytoalexins" and Part XX of "Synthetic Studies of Rishitin and Related Compounds." Part XXXIX and XIX of the respective series, A. Murai, S. Sato, and T. Masamune, Bull. Chem. Soc. Jpn., in press.

2) A. Murai, N. Katsui, F. Yagihashi, T. Masamune, Y. Ishiguri, and K. Tomiyama, J. Chem. Soc., Chem. Commun., 1977, 670.

3) A. Murai, K. Nishizakura, N. Katsui, and T. Masamune, Tetrahedron Lett., 1975, 4399; Bull. Chem. Soc. Jpn., 50, 1206 (1977).

4) G. C. Andrews and T. C. Crawford, Tetrahedron Lett., 21, 693 (1980).

5) All attempts to form the 2,3-acetonide of 10 failed, even with the Wako gel Q-23 available recently.[3]

6) Cf., S. K. Chaudhary and O. Hernandez, Tetrahedron Lett., 1979, 95.

7) T. Masamune, A. Murai, M. Takasugi, A. Matsunaga, N. Katsui, N. Sato, and K. Tomiyama, Bull. Chem. Soc. Jpn., 50, 1201 (1977).

8) MS, m/z 224 (M^+), 206, 205, and 191; IR (CCl_4), 3410, and 1075 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ 1.14 (3H, d, J = 6.8 Hz), 1.73 (3H, s), 3.20 (1H, t, J = 9.0 Hz), and 3.64 (1H, dt, J = 6.4 and 9.8 Hz).

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