Tetrahedron Letters No. 35, pp 3301 - 3304. 0040-4039/78/0822-3301$02.00/0

SYNTHESES OF (+) AND (-) TETRAHYDROCERULENIN FROM D-XYLOSE REVISED STEREOCHEMISTRY OF NATURAL (+) CERULENIN

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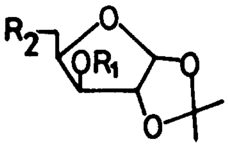
The natural antifungal antibiotic (+) cerulenin[1] has received considerable attention as an inhibitor of the biosynthesis of fatty acids and steroids[2] as well as compounds formed through the polyketide pathway like macrolide antibiotics[3] and aromatic products[4]. Because of this remarkable set of biological properties, a fierce synthetic move was recently observed and resulted in three independent and convergent syntheses of racemic cerulenin[5]. Hydrogenation of the natural product over platinum catalyst gave microbiologically active (+) tetrahydrocerulenin, the racemic form of which has also been synthesized[5b].

This communication reports the first chemical synthesis of the two optically active enantiomers of tetrahydrocerulenin.

Treatment of 1,2-O-isopropylidene-5-O-p-toluenesulfonyl-α-D-xylofuranose 1[6] with heptyl magnesium bromide (7 eq.) in the presence of dilithium tetrachlorocuprate[7] gave compound 2[8], m.p. 73-75°, $\{\alpha\}_{D}^{20}$ -17.7° (c 0.65, $CHCl_3$), which was directly converted (benzoyl chloride-pyridine) into benzoate 3 (77% from 1), $\{\alpha\}_{D}^{20}$-24.8° (c 1.64, $CHCl_3$). Acid hydrolysis (trifluoroacetic acid-water,9:1,v/v,-10°C,1.5h) gave 3-O-benzoyl-5-C-heptyl-5-deoxy-D-xylofuranose 5 (69%), $\{\alpha\}_{D}^{20}$+ 4.1° (c 6.68, $CHCl_3$). Treatment of 5 with methanesulfonyl chloride (2.2 eq.) and diisopropylethylamine in dichloromethane (5 min at room temperature) provided the chloride 6 which was immediately and smoothly converted into 7 (silver oxide-silver perchlorate in acetone-water, room temperature, 12 h) (77% from 5), $\{\alpha\}_{D}^{20}$ + 34.9° (c 1.32, $CHCl_3$). Treatment of 7 with sodium methoxide in methanol-THF (0°C, 10 min) provided the anhydro sugar 8 (75 %), m.p. 67.5-68°C (hexane), $\{\alpha\}_{D}^{20}$-1.5° (c 0.93, $CHCl_3$). Oxidation with Collins reagent[9] gave the epoxy lactone 9 (95%), m.p. 55° C (hexane), $\{\alpha\}_{D}^{20}$ -38.3° C (c 0.76, $CHCl_3$). Ammonolysis of 9 with ammonium

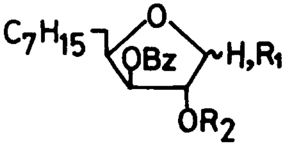


1 R_1 = H R_2 = OTs

2 R_1 = H R_2 = C_7H_{15}

3 R_1 = Bz R_2 = C_7H_{15}

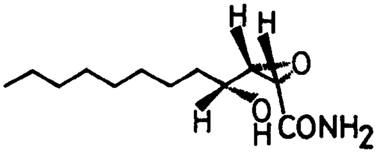
4 R_1 = Ms R_2 = C_7H_{15}



5 R_1 = OH , R_2 = H

6 R_1 = Cl , R_2 = Ms

7 R_1 = OH , R_2 = Ms



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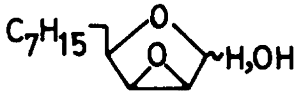

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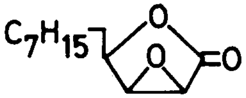

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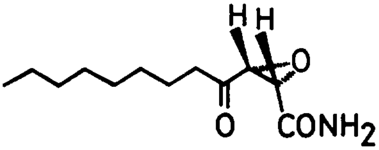

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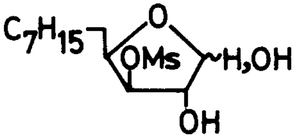

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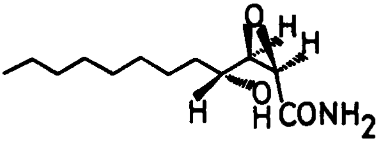

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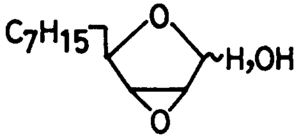

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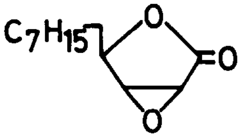

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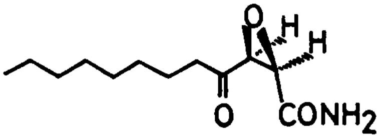

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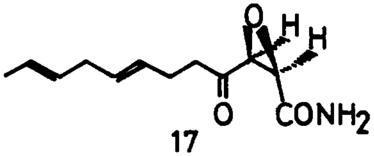

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hydroxide in methanol (room temperature, 2.5 h) led to the hydroxy-epoxy amide 10 (98 %), m.p. 154° C (acetone), $\{\alpha\}_{D}^{20}$+ 5.9° (c 0.59, methanol). The final conversion of amido alcohol 10 to (2S)(3R) tetrahydrocerulenin 11 was effected by treatment with Collins reagent[9] (25° C, 3 h) (100 %), m.p. 84.5-85° C (CCl_4), $\{\alpha\}_{D}^{20}$ -52° (c 1.02, MeOH, after 24 h)[10].

In order to prepare the enantiomer of 11 , the acetal 2 was mesylated (methanesulfonyl chloride-triethylamine in dichloromethane, 0°C, 1.5 h) to give 4 (73 % from 1), $\{\alpha\}_{D}^{20}$-17° (c 2.32, $CHCl_3$). Acid hydrolysis (trifluoroacetic acid-water,9:1,v/v, 0° C,1h) gave 3-O-methanesulfonyl-5-C-heptyl-5-deoxy-D-xylofuranose 12 (73 %), m.p. 52.5-53.5° C (CCl_4), $\{\alpha\}_{D}^{20}$ + 19.4° (c 1.25, $CHCl_3$). Treatments similar to those previously described from 7 successively provided : 13:(70 %), m.p. 39° C (hexane-pentane), $\{\alpha\}_{D}^{20}$-22° (c 0.47, $CHCl_3$); 14 :(89 %), m.p. 32.5° C (hexane-petroleum ether 40-60°), $\{\alpha\}_{D}^{20}$ + 59° (c 0.14, $CHCl_3$)[11]; 15 : (97 %), m.p. 104° C (acetone-hexane)[12], $\{\alpha\}_{D}^{20}$+ 12° (c 0.31, MeOH); (2R)(3S) tetrahydrocerulenin 16:(96 %), m.p. 84° C (CCl_4), $\{\alpha\}_{D}^{20}$+ 52° (c 1.0, MeOH, after 24 h)[10].

The date reported[12] for (+) tetrahydrocerulenin derived from natural (+) cerulenin are : m.p. 85.5-86.5° (CCl_4), $\{\alpha\}_{D}^{25}$+ 43° ± 3 (c 0.25, MeOH, after 24 h).

The absolute configuration of (+) tetrahydrocerulenin and, as a consequence, of natural (+) cerulenin 17 is thus (2R)(3S) and not (2S)(3R) as previously reported[13].

The synthesis of (+) tetrahydrocerulenin described herein is characterized by its simplicity and efficiency, and is a new example of the interest of carbohydrates as chiral intermediates in organic synthesis of optically active natural products.

Acknowledgment. This research was partially supported by Centre National de la Recherche Scientifique to whom we are grateful. We thank Dr. Tishler for providing us with various synthetic materials.

REFERENCES AND NOTES

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8. Satisfactory elemental analyses and i.r. and n.m.r. data have been obtained for all intermediates and products.
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10. ^{1}H n.m.r., i.r. and t.l.c. (silica gel) were identical with synthetic racemic tetrahydrocerulenin (which has been shown to be identical with natural tetrahydrocerulenin) kindly provided to us by Dr. Max Tishler.
11. It is interesting to compare n.m.r. data (90 MHz, CCl_4) of the epoxy lactones 10 and 15. 10 : δ 0.90 (t,3H,CH_3-$(CH_2)_7$-), 1.10-1.95 (m,14H), 3.63 (d,1H,$J_{2,3}$2.4Hz, H-2), 3.98 (dd,1H,$J_{3,4}$1.3Hz,H-3), 4.36 (dt,J_{4,CH_2}6.9Hz,H-4); 15 : δ 0.90 (t,3H,CH_3-$(CH_2)_7$-), 1.10-1.95 (m,14H), 3.65 (dd,1H,$J_{2,3}$2.3Hz,$J_{3,4}$0.7Hz,H-3), 3.90 (d,1H,H-2), 4.46 (dt, J_{4,CH_2}6.3Hz,H-4). In accordance with Tishler's results[5b], $J_{3,4}$ is very small (0.7Hz) when the epoxide and the side chain are trans (10 and 15 are numbered as carbohydrates).
12. A.A. Jakubowski et al.[5b] reported m.p. 106-107° (CCl_4) for the racemic form. N.m.r. and t.l.c. (silica gel) data of both compounds are identical.
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(Received in UK 25 May 1978; accepted for publication 3 July 1978)