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A TOTAL SYNTHESIS OF NATURAL CERULENIN FROM D-GLUCOSE

M. Pietraszkiewicz and P.Sinaÿ*

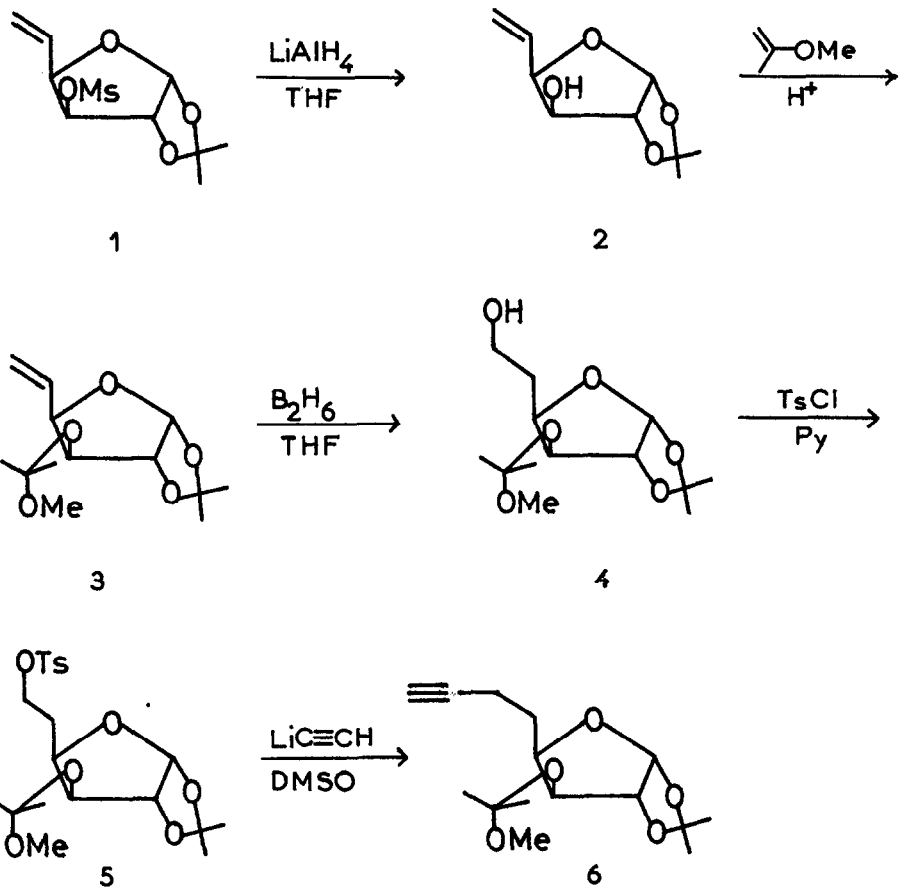
Laboratoire de Biochimie Structurale, E.R.A. 739,

U.E.R. de Sciences Fondamentales et Appliquées, 45045 Orléans Cédex, France.

D-glucose has served as a chiral synthon in a total synthesis of the fungal metabolite cerulenin.

The fungal metabolite cerulenin 14 possesses a very interesting spectrum of biological activities[1] and three total syntheses of dl-cerulenin have been reported[2]. On the other hand, two independent syntheses of (+) and (-) tetrahydrocerulenin from carbohydrates have been recently achieved[3], resulting in a new assignment of the absolute configuration of the molecule as that shown . This letter describes a total synthesis of natural cerulenin 14 from D-glucose.

The mesylate 1 is easily available[4] from D-glucose and was used as the starting chiral synthon. Treatment of 1 with lithium aluminum hydride in tetrahydrofuran (50°C, 4h) gave the known[5] alcohol 2 (81 %),m.p. 63° C (ether-hexane), which was quantitatively converted (2-methoxypropene in chloroform with one drop of trifluoroacetic acid) into 3, $\{\alpha\}_D^{20}$-16° (c 2.58, hexane). Hydroboration of 3 (diborane-THF, 0°C,10 h) provided the alcohol 4 (69 %), $\{\alpha\}_D^{20}$-8° (c 1.29, $CHCl_3$), which was directly converted (p-toluenesulfonyl chloride-pyridine) into tosylate 5 , $\{\alpha\}_D^{20}$-10° (c 2.15, $CHCl_3$), then (ethylene diamine complex of lithium acetylide-DMSO, 15° C, 1h) into 6 (42% from 4),$\{\alpha\}_D^{20}$ -4° (c 3.18, hexane)[6]. The lithio derivative of 6 (PhLi-THF) was coupled with trans-crotyl chloride in the presence of a catalytic amount of sodium iodide (20°,12h) and the resulting acetylenic compound ($\{\alpha\}_D^{20}$-3° in hexane) was reduced (lithium-liquid ammonia-t-butanol-ammonium sulfate, 20min) to trans-trans 7 (90 % from 6),$\{\alpha\}_D^{20}$-16° (c 3.16, hexane). Acid hydrolysis (trifluoroacetic acid-chloroform-methanol) gave the alcohol 8 (99 %),$\{\alpha\}_D^{20}$-20° (c 3.36,$CHCl_3$). Acid hydrolysis (trifluoroacetic acid-water,9:1,20° C, 40 min) of 9 (obtained after treatment of alcohol 8 with methylsulfonyl chloride in pyridine) gave compound 10 (83%), $\{\alpha\}_D^{20}$+ 21° (c 3.17,$CHCl_3$). Treatment of 10 with sodium methoxide in THF provided the anhydro



sugar 11 (65%), $\{\alpha\}_D^{20}$-20° (c 1, $CHCl_3$). Oxidation with Collins reagent[7] gave the lactone 12 (88 %), $\{\alpha\}_D^{20}$+ 45° (c 2.44 ,$CHCl_3$). Ammonolysis of 12 with ammonium hydroxide in methanol (room temperature, 30 min) led to the amide 13 (90%),$\{\alpha\}_D^{20}$+ 70° (c 1.66 ,$CHCl_3$). The final conversion of amido alcohol 13 into natural cerulenin 14 was effected by treatment with Collins reagent[7] (25°C,4h) (90%), m.p. 93° C(benzene),$\{\alpha\}_D^{20}$-10° (c1,$CHCl_3$)[8]. Compound 6 may by regarded as a useful synthon for the preparation of various analogs of natural cerulenin. This work is now in progress in our laboratory.

Acknowledgment

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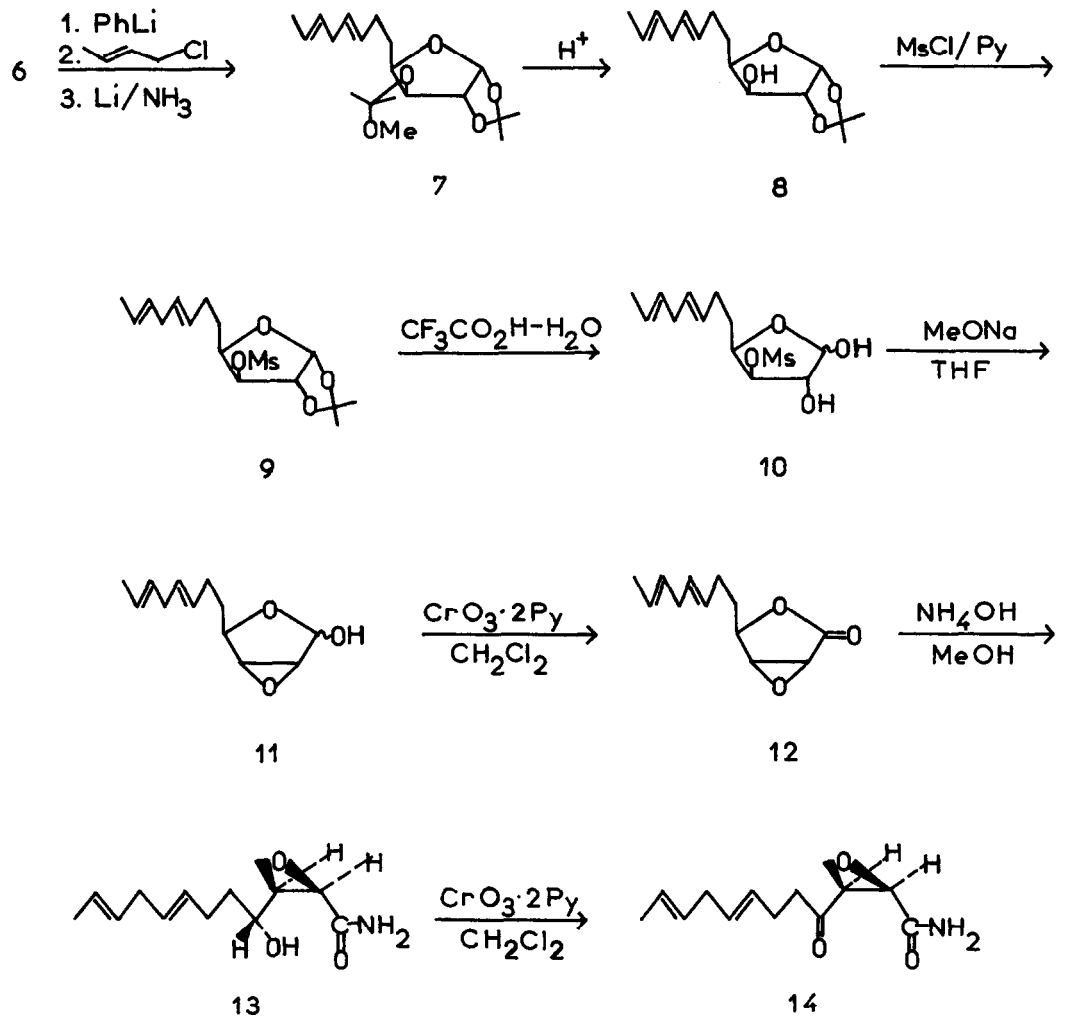

7 8 9 10 11 12 13 14

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2. (a) R.K. Boeckman, Jr. and E.W. Thomas, J.Am.Chem.Soc., 101,978 (1979);(b) A.A.Jakubowski F.S. Guziec,Jr. and M.Tishler, Tetrahedron Lett., 2399 (1977); (c) E.J. Corey and D.R. Williams, Tetrahedron Lett., 3847 (1977).
3. H.Ohrui and S. Emoto, Tetrahedron Lett., 2095 (1978); J.R. Pougny and P.Sinaÿ, ibid, 3301 (1978).
4. J.K.N. Jones and J.L. Thompson, Can.J.Chem., 35,955 (1957) and references cited.
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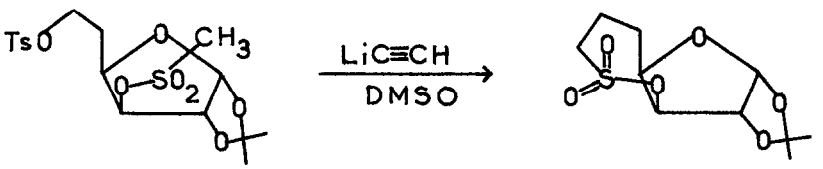
6. Ethynylation was initially attempted on easily available 5-deoxy-1,2-O-isopropylidene-3-O-methylsulfonyl-6-O-p-toluenesulfonyl-α-D-glucofuranose, but resulted only in high yield cyclization according to the following scheme :



7. J.C. Collins, W.W. Hess and F.J. Franck, Tetrahedron Lett., 3363 (1968).

8. ^{1}H n.m.r. and i.r. were identical with natural cerulenin. Selected n.m.r. characteristics are summarized here : 1 (acetone-d_6) δ 1.31 and 1.47 (6H,2s), 3.17 (3H,s), 4.85 (1H,d , $J_{1,2}$4Hz,H-2),4.96(1H,$J_{3,4}$3.5Hz,H-3), 6.01 (1H,d,H-1);2 ($CDCl_3$) δ 1.32 and 1.50 (6H,2s), 2.19 (1H,d,OH), 4.10 (1H,dd,$J_{3,4}$4Hz,$J_{3,OH}$5Hz,H-3), 4.57 (1H,d,$J_{1,2}$4Hz,H-2), 5.95 (1H,d, H-1); 3 ($CDCl_3$) δ 1.25,1.32 and 1.41 (12H), 3.13 (3H,s), 4.13 (1H,d,$J_{3,4}$4Hz,H-3),4.42 (1H,d,$J_{1,2}$4Hz,H-2), 5.80 (1H,d,H-1); 6 (CCl_4)δ 1.20 and 1.50 (12H), 1.70-2.00 (3H,m), 2.20-2.50 (2H,m), 3.20 (3H,s), 4.00-4.30 (2H,m,H-3 and H-4),4.45 (1H,d,$J_{1,2}$4Hz,H-2),5.70 (1H,d,H-1); 7 (CCl_4) δ 1.50-1.70 (5H,m), 1.90-2.30 (2H,m), 2.50-2.80 (2H,m), 3.18 (3H,s), 3.90-4.10 (2H,m,H-3 and H-4),4.45 (1H,d,$J_{1,2}$4Hz,H-2), 5.30-5.50 (4H,m), 5.70 (1H,d,$J_{1,2}$ 4Hz,H-1); 8 ($CDCl_3$) δ 1.30 and 1.48 (6H,2s), 2.60-2.85 (2H,m), 3.95-4.25 (2H,m), 4.50 (1H,d,$J_{1,2}$4Hz,H-2), 5.35-5.60 (4H,m), 5.90 (1H,d,H-1);9 (CCl_4) δ1.45 and 1.30 (6H,2s), 1.55-1.90 (5H,m), 2.00-2.30 (2H,m), 2.60-2.85 (2H,m), 3.02 (3H,s), 4.10-4.30 (1H,m,H-4), 4.70 (1H,d,$J_{1,2}$4Hz,H-2),4.83 (1H,d,$J_{3,4}$2.5Hz,H-3),5.30-5.60 (4H,m), 5.83 (2H,d,H-1); 11 (CCl_4)δ 1.55-1.80 (5H,m),2.00-2.40(2H,m), 2.60-2.90(2H,m), 3.30 (1H,s,OH),3.48-3.70 (2H,m,H-2 and H-3), 4.02 (1H,t,H-4), 5.30-5.55 (4H,m);12 (CCl_4) δ 1.60-1.90 (5H,m),2.10-2.40 (2H,m), 2.60-2.90 (2H,m), 3.67 (1H,d,H-3), 3.91 (1H,d,$J_{2,3}$3Hz,H-2), 4.56 (1H,t,H-4); 13 ($CDCl_3$) δ 3.60 (2H,m,H-2 and H-3), 5.30-5.70 (4H,m), 6.30 (2H,s,amide).

Note added on proof : during the examination of this manuscript by referees, a similar synthesis has been reported : N.Sueda,H.Ohrui and H. Kuzukara,Tetrahedron Lett., 2039 (1979).

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