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STEREOSELECTIVE SYNTHESIS OF (+)- AND (-)-TETRAHYDROCERULENIN FROM D-GLUCOSE THE CORRECT ABSOLUTE CONFIGURATION OF NATURAL CERULENIN

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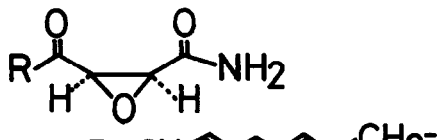
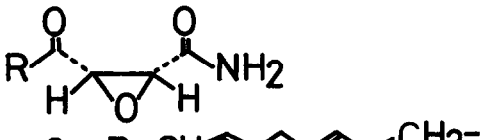
Cerulenin, an antibiotic active against a number of bacteria and fungi,[1] was isolated from the culture filtrate of Cephalosporium caerulens in 1960 by Hata and coworkers.[2] It has attracted considerable attention because of its inhibitory action in the biosynthesis of lipids and steroids.[3,4,5] The structure of cerulenin has been assined as 2S,3R-epoxy-4-oxo-7,10-trans,trans-dodecadienoic acid amide 1a by Ōmura et al.[6,7] Very recently three different syntheses of racemic cerulenin and its derived, microbiologically active, tetrahydrocerulenin 1b have been reported.[8,9,10]

As a part of our studies on the stereoselective syntheses of biologically active compounds in optically active forms by use of asymmetric carbons of carbohydrates[11], the synthesis of cerulenin and its derivatives were undertaken. This communication describes a synthesis of optically active tetrahydrocerulenin 1b and its antipode 2b from D-glucose and the correct absolute configuration of cerulenin.

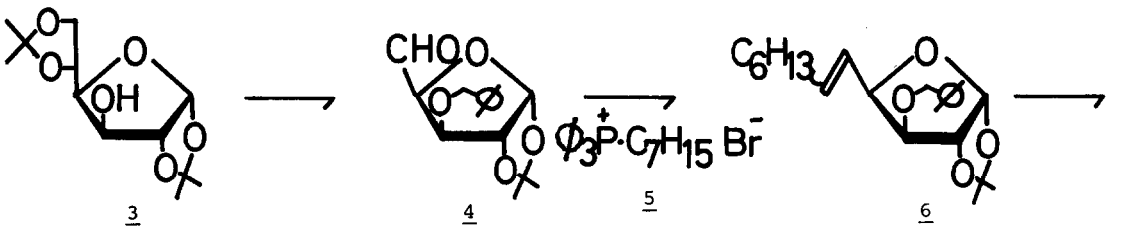


1a R=CH_3
1b R=n-C_8H_{17}

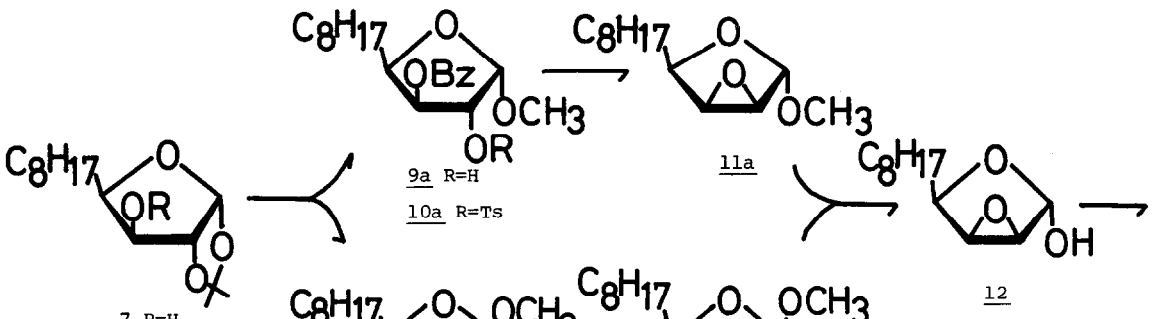


2a R=CH_3
2b R=n-C_8H_{17}

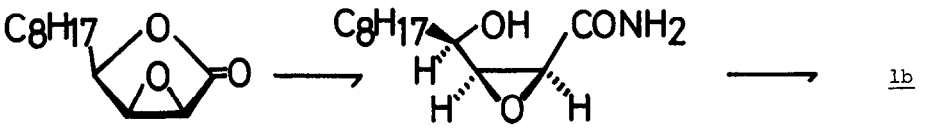
The starting material 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3 was converted to the aldehyde 4 according to the well known procedure.[12] Treatment of 4 with phosphonium salt 5[13] in DMSO in the presence of sodium methylsulfinylmethide[14] gave a syrupy 6[67%, $[\alpha]_D^{20}$ -78.5° (c 0.9, $CHCl_3$)]. Catalytic reduction of 6 over 10% Pd-C in acetic acid gave a syrupy alcohol 7[97%, $[\alpha]_D^{20}$ -21.0° (c 0.15, $CHCl_3$)]. Benzoylation of 7 gave a syrupy benzoate 8[95%, $[\alpha]_D^{20}$ -24.5° (c 0.16, $CHCl_3$)]. Treatment of 8 with 1% methanolic hydrogen chloride at reflux for 3 hr gave an anomeric mixture of methy D-xylo-furanoside derivative 9a and 9b[9a: 38%, syrup, $[\alpha]_D^{20}$ +80.4° (c 0.17, $CHCl_3$), nmr($CDCl_3$) δ 5.04(1H, d, $J_{1,2}$=4Hz, H-1). 9b: 47%, syrup, $[\alpha]_D^{20}$ +64.7° (c 0.12, $CHCl_3$), nmr($CDCl_3$) δ 4.87(1H, d, $J_{1,2}$=2Hz, H-1)], which were tosylated to give the corresponding tosylate 10a and 10b, respectively[10a: 96%, mp 98-100°C, $[\alpha]_D^{20}$ +135.5° (c 0.7, $CHCl_3$), 10b: 95%, mp 98-100°C, $[\alpha]_D^{20}$ +12.1° (c 0.14, $CHCl_3$)]. Treatment of 10a and 10b with $NaOCH_3$ in CH_2Cl_2 gave the corresponding epoxide 11a and 11b, respectively[11a: quantitative,



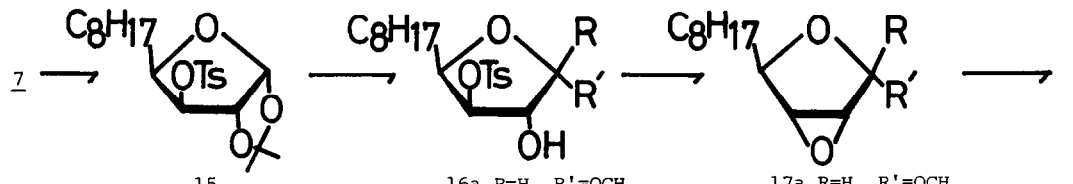
3 4 5 6



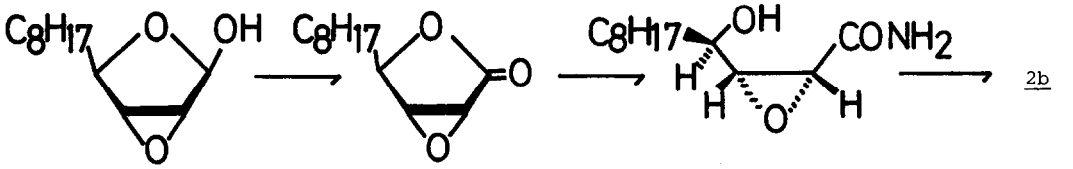
9a R=H
10a R=Ts
11a
7 R=H
8 R=C_6H_5CO
12
9b R=H
10b R=Ts
11b



13 14 1b



7 15 16a R=H, R'=OCH_3
16b R=OCH_3, R'=H
17a R=H, R'=OCH_3
17b R=OCH_3, R'=H



18 19 20 2b

mp 50°C, $[\alpha]_D^{20}$ +55.5° (c 0.2, $CHCl_3$), nmr($CDCl_3$) δ0.88(3H, t, J=6Hz, $-CH_2\underline{CH_3}$), 1.10-1.80(14H, m, methylene protons), 3.41(3H, s, OCH_3), 3.60(2H, s, H-2, H-3), 3.98(1H, t, $J_{4,5}$=6Hz, H-4), 4.91(1H, s, H-1). 11b: quantitative, syrup, $[\alpha]_D^{20}$ -49.6° (c 0.14, $CHCl_3$), nmr($CDCl_3$) δ0.88(3H, t, J=6Hz, $-CH_2\underline{CH_3}$), 1.10-1.90(14H, m, methylene protons), 3.50(3H, s, OCH_3), 3.58(1H, d, $J_{2,3}$= 4Hz, H-3), 3.65(1H, d, H-2), 3.86(1H, t, $J_{4,5}$=6Hz, H-4), 4.96(1H, s, H-1). Treatment of 11a and 11b with 80% aqueous acetic acid at 100°c overnight gave a lactol 12[60%, mp 64-65°C, $[\alpha]_D^{20}$ -1.6° (c 1.0, $CHCl_3$), nmr($CDCl_3$) δ0.88(3H, t, J=6Hz, $-CH_2\underline{CH_3}$),1.10-1.90(14Hz, m, methylene protons), 3.64(2H, s, H-2, H-3), 4.10(1H, t, $J_{4,5}$=6Hz, H-4), 5.39(1H, s, H-1)]. Collins oxidation[15] of 12 gave a crystalline epoxy lactone 13[93%, mp 54-55°C, $[\alpha]_D^{20}$ -37.5° (c 0.2, $CHCl_3$)]. Ammonolysis of 13 with ammonium hydroxide in methanol gave the hydroxy-cis-epoxy amide 14[85%, mp 146-148°C, $[\alpha]_D^{20}$ +4.1° (c 0.6, MeOH)], which was converted into 2S,3R-tetrahydrocerulenin 1b by oxidation with Collins reagent[15] in 95% yield. The resulting 1b, mp 85-86°C(CCl_4), had a nmr completely identical with that of an authentic tetrahydrocerulenin[6], however, it had a rotation of $[\alpha]_D^{20}$ -53.8° (c 0.15, MeOH, after 24 hr) that was a similar magnitude but in the opposite sign as was reported for the authentic sample: $[\alpha]_D^{25}$ +43°±3 (c 0.25, MeOH, after 24 hr). These results indicate that the absolute configuration of cerulenin would be 2R,3S-epoxy-4-oxo-7,10-trans,trans-dodecadienoic acid 2b.

In order to confirm the absolute configuration of cerulenin, the stereoselective synthesis of 2b, the antipode of 1b, was carried out. Compound 7 was converted into the tosylate 15[95%, syrup, $[\alpha]_D^{20}$ -29.6° (c 0.1, $CHCl_3$)], which was treated with methanolic hydrogen chloride to give a mixture of 16a and 16b[16a: 43%, syrup, $[\alpha]_D^{20}$ +77.0° (c 0.2, $CHCl_3$), 16b: 45%, syrup, $[\alpha]_D^{20}$-11.3° (c 0.15, $CHCl_3$)]. Treatment of 16a and 16b with $NaOCH_3$ in CH_2Cl_2 gave the corresponding epoxide 17a and 17b, respectively[17a: 97%, mp 32-33°C, $[\alpha]_D^{20}$ +31.7° (c 0.7, $CHCl_3$), 17b: 96%, syrup, $[\alpha]_D^{20}$ -67.9° (c 0.9, $CHCl_3$)]. Treatment of 17a or 17b with 70% aqueous acetic acid at 100°C overnight gave the epoxy lactol 18[70%, mp 37-38°C, $[\alpha]_D^{20}$ -26.7° (c 0.7, $CHCl_3$)], which was converted into the epoxy lactone 19[95%, mp 30-31°C, $[\alpha]_D^{20}$ +45.2° (c 0.8, $CHCl_3$)]. Ammonolysis of 19 with ammonium hydroxide in methanol gave the hydroxy-cis-epoxy amide 20[90%, mp 101-102°C, $[\alpha]_D^{20}$+48.3° (c 0.5, MeOH)]. Collins oxidation of 20 gave the 2R,3S-tetrahydrocerulenin 2b[94%, mp 86-87°C, $[\alpha]_D^{20}$ +44.4° (c 0.25, MeOH, after 24 hr)].[16] The physical and chemical properties of 2b were completely identical with those of an authentic tetrahydrocerulenin. Therefore, the absolute configuration of cerulenin should be revised as 2R,3S-epoxy-4-oxo-7,10-trans,trans-dodecadienoic acid amide 2a.

The synthesis of optically active cerulenin and its derivatives by the similar route are now in progress in our laboratory.

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16. Satisfactory elemental analyses were obtained for all compounds.