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# STEREOSELECTIVE SYNTHESIS OF (+)-CERULENIN FROM D-GLUCOSE

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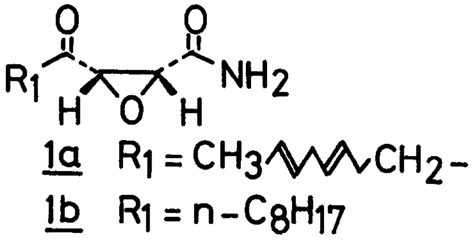
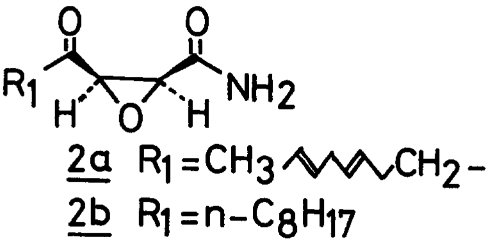
Summary: (+)-Cerulenin 1a was synthesized stereoselectively from D-glucose.

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 had been assigned as 2S,3R-epoxy-4-oxo-7,10-trans,trans-dodecadienoic acid amide 2a by Ōmura et al.[6,7] and very recently it was revised as 2R,3S-epoxy-4-oxo-7,10-trans,trans-dodecadienoic acid amide 1a by us[8] and Sinay et al.[9] independently based on the stereoselective synthesis of (+)- and (-)-tetrahydrocerulenin(1b and 2b) from carbohydrate precursors. Though three different syntheses of racemic cerulenin have been reported,[10,11,12] we would like to describe in this communication the first stereoselective synthesis of (+)-cerulenin from D-glucose as a part of our studies on the chiral synthesis of biologically active compounds from carbohydrate precursors.[13]



1a $R_1 = CH_3$〰〰$CH_2$-
1b $R_1 = n\text{-}C_8H_{17}$

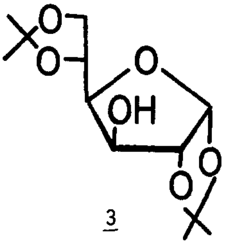


2a $R_1 = CH_3$〰〰$CH_2$-
2b $R_1 = n\text{-}C_8H_{17}$

The starting material 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3 was converted to the aldehyde 4 according to the known procedure.[14] Treatment of 4 with methyl diethylphosphonoacetate in ether in the presence of sodium hydride gave a syrupy 5[77%, $[\alpha]_D^{20}$-32.7°(c=1.0, $CHCl_3$)]. Catalytic reduction of 5 over 10% Pd-C in ethanol gave a syrupy saturated ester 6[97%, $[\alpha]_D^{20}$-43.4°(c=1.0,$CHCl_3$)], which was reduced with LAH in ether to afford a syrupy alcohol

7[83%, $[\alpha]_D^{20}$-51.4°(c=1.0,$CHCl_3$)]. Oxidation of 7 with DMSO and oxalyl chloride in $CH_2Cl_2$[15] at -60° gave an aldehyde 8, which was directly treated with a mixture of triphenyl phosphine, $CBr_4$ and Zn powder in $CH_2Cl_2$[16] to give a dibromoolefin 9[90% from 6]. Treatment of 9 with two eq. n-BuLi in THF[16] gave, after hydrolysis, an acetylenic compound 10 as syrup[88%, $[\alpha]_D^{20}$ -53.9°(c=1.2,$CHCl_3$)]. Treatment of 10 with 2.5 eq. EtMgBr in THF(60°, 1h), followed by the treatment with crotyl bromide in the presence of catalytic amount of $Cu_2Cl_2$ at room temperature overnight gave a syrupy 11[94%, $[\alpha]_D^{20}$-55.5°(c=1.0, $CHCl_3$)].

Conversion of 11 to 15 turned out to be a most troublesome undertaking. At first it was expected that 11 could be converted directly to 15 under the Birch reduction condition. However, treatment of 11 with more than 2 eq. Li in liq.$NH_3$ under a variety of conditions gave a complex mixture because of overreduction and/or isomerization of the side chain double bonds. Therefore, the reduction was carried out stepwise. Treatment of 11 with 1.9 eq. Li in a mixture of liq.$NH_3$ and THF at -78° in the presence of 0.5 eq. t-BuOH and 5 eq. $(NH_4)_2SO_4$ gave 12(73%, mp 82.0°, $[\alpha]_D^{20}$+19.4°(c=0.7, $CHCl_3$)] and unreacted 11(22%). Treatment of 12 with dihydropyran in the presence of pyridinium p-toluenesulfonate(PPTS)[17] in $CH_2Cl_2$ gave syrupy 13[quantitative, $[\alpha]_D^{20}$-50.8°(c=1.0,$CHCl_3$)]. Reduction of 13 with 3 eq. Li under similar conditions for the synthesis of 12 gave, after purification by a column chromatography on silicic acid coated with $AgNO_3$ , 14 as syrup[80%, $[\alpha]_D^{20}$-42.5°(c=1.0, $CHCl_3$)]. Treatment of 14 with PPTS[17] in EtOH gave a syrupy 15[88%, $[\alpha]_D^{20}$-14.4°(c=1.0, $CHCl_3$)]. Treatment of 15 with mesyl chloride in the presence of $Et_3N$ in $CH_2Cl_2$ at 0° gave 16[93%, $[\alpha]_D^{20}$-22.6°(c=1.0, $CHCl_3$)]. Acid hydrolysis($CF_3COOH$-$H_2O$, 9:1, 0°, 2.5h) of 16 gave syrupy 17 [72%, $[\alpha]_D^{20}$+25.3°(c=0.7,$CHCl_3$)] which was treated with $NaOCH_3$ in THF at 0° to give an epoxide 18 as syrup[72%, $[\alpha]_D^{20}$-20.2°(c= 0.85,$CHCl_3$, after 5h)]. Oxidation of 18 with pyridinium chlorochromate[18] in $CH_2Cl_2$ gave an epoxylactone 19[70%, $[\alpha]_D^{20}$+56.5°(c=0.8, $CHCl_3$)]. Ammonolysis of 19 with methanolic ammonium hydroxide led to the hydroxy epoxyamide 20 quantitatively, which was oxidized with pyridinium chlorochromate[18] in $CH_2Cl_2$ to give (+)-cerulenin 1a[60%, mp 93°, $[\alpha]_D^{20}$+62.0°(c=0.15, MeOH)]. The physical and chemical properties of 1a were completely identical with those of an authentic sample.[19]



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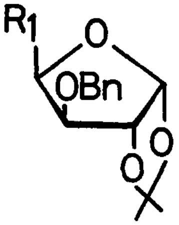


4 $R_1$= CHO

5 $R_1$= CH=CHCOOMe

6 $R_1$= $CH_2CH_2COOMe$

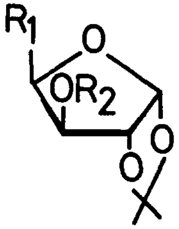
7 $R_1$= $CH_2CH_2CH_2OH$

8 $R_1$= $CH_2CH_2CHO$

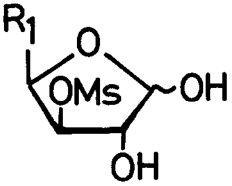
9 $R_1$= $CH_2CH_2CH{=}CBr_2$

10 $R_1$= $CH_2CH_2C{\equiv}CH$

11 $R_1$= $CH_2CH_2C{\equiv}CCH_2CH\overset{t}{=}CHCH_3$



| | | |
|---|---|---|
| 12 | $R_1$= $CH_2CH_2C{\equiv}CCH_2CH\overset{t}{=}CHCH_3$ | $R_2$= H |
| 13 | $R_1$= ,, | $R_2$= THP |
| 14 | $R_1$= $CH_2CH_2CH\overset{t}{=}CHCH_2CH\overset{t}{=}CHCH_3$ | $R_2$= THP |
| 15 | $R_1$= ,, | $R_2$= H |
| 16 | $R_1$= ,, | $R_2$= Ms |



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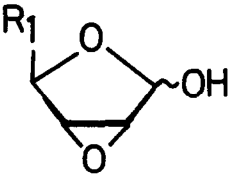

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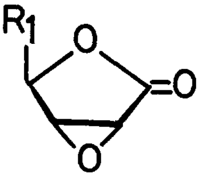

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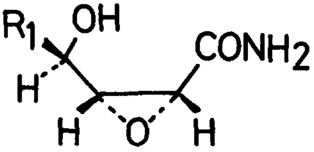

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$R_1$= $CH_2CH_2CH\overset{t}{=}CHCH_2CH\overset{t}{=}CHCH_3$

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19. We are indebted to Prof. Dr. S. Ōmura for an authentic sample.
20. Satisfactory elemental analyses were obtained for all compounds.

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