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SYNTHESIS OF D-ERYTHRO-1-DEOXYDIHYDROCERAMIDE-1-SULFONIC ACID

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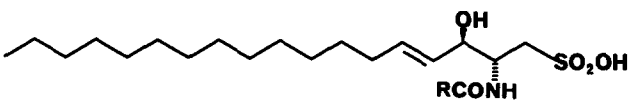
Abstract: New D-erythro-1-deoxydihydroceramide-1-sulfonic acid, isolated from alkali-stable lipids in a non-photosynthetic marine diatom Nitzschia alba, was synthesized from galactose as a chiral precursor using the Hanessian-Hullar reaction as the key step in the reaction sequence.

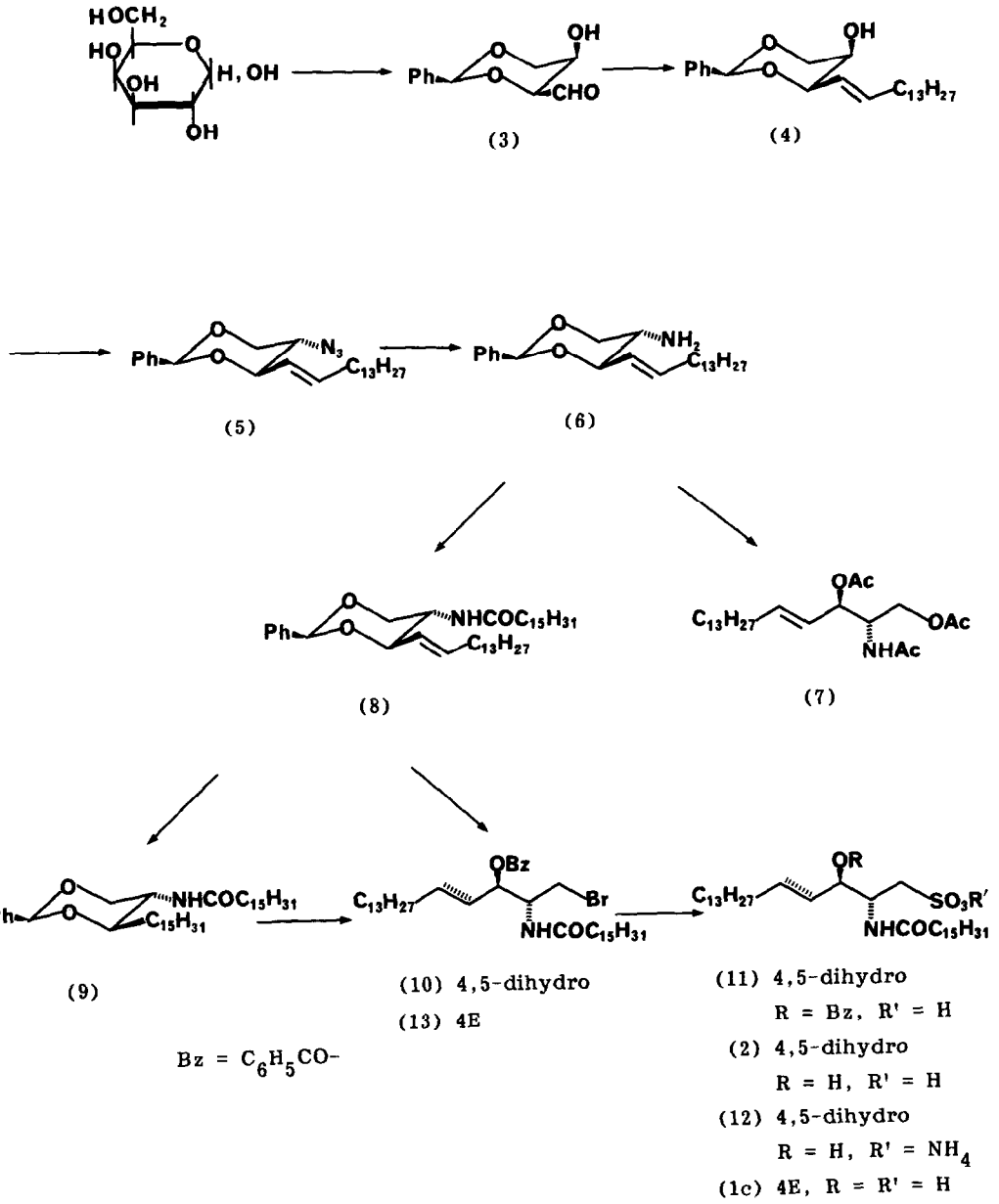
New sulfolipids were isolated[1] by one of the authors (M.K.) from the alkali-stable lipids in a non-photosynthetic marine diatom Nitzschia alba and their structures were determined spectrometrically and by identification of their hydrolysis products as 1-deoxyceramide-1-sulfonic acids (DCS), (1).



(1a) : R = $C_{13}H_{27}$
(1b) : R = $C_{13}H_{25}$
(1c) : R = $C_{15}H_{31}$
(1d) : R = $C_{15}H_{29}$ (3E)
(2) : R = $C_{15}H_{31}$; 4,5-dihydro

Although the structure, but not its stereochemistry, was clarified almost 10 years ago, there has been no reported synthesis. We decided to find an efficient way to prepare this compound which would enable the determination of its molecular structure and provide authentic samples for lipid research. In designing our approach to DCS we set as our first target a saturated D-erythro-DCS, (2), partly because DCS has a stereochemistry (C-2 and -3) similar to that of sphingosine and partly because dihydro-DCS could be obtained in relatively pure form by hydrogenation of a mixture of natural sulfolipids.[2] The first synthesis of (2) is reported herein.

Of the many methods for synthesizing sphingosine,[3] the required intermediate (8) could be prepared efficiently by modification of Schmidt's procedure[4] using galactose as a starting material. Thus galactose was converted into hydroxy aldehyde (3) by partial acetalization with benzaldehyde and anhydrous zinc chloride followed by periodate oxidation. Schmidt et al., reported that the Schlosser's modification of Wittig reaction to (3) exclusively gave trans


HOCH2
HO
OH
H, OH
OH
Ph
OH
CHO
OH
C13H27
(3)
(4)
N3
NH2
(5)
(6)
NHCOC15H31
(8)
OAc
NHAc
(7)
OBz
Br
OR
SO3R'
(9)
(10) 4,5-dihydro
(13) 4E
(11) 4,5-dihydro
R = Bz, R' = H
(2) 4,5-dihydro
R = H, R' = H
(12) 4,5-dihydro
R = H, R' = NH4
(1c) 4E, R = R' = H
Bz = C6H5CO-

Scheme I

olefin (4). But we did not observe the trans selectivity and thus used the usual Wittig reaction and photo-isomerization sequence. The hydroxyaldehyde (3) was converted into trans olefin (4) in 56% yield by Wittig reaction ($C_{14}H_{29}PPh_3^+Br^-$, t-BuOK, THF, 0°C; cis:trans 4:1, GLC) followed by photoisomerization[5] using high pressure mercury lamp in the presence of diphenyldisulfide (cis:trans 1:10, GLC). The olefin alcohol (4) was transformed into amine (6) by the following reaction sequence: (i) mesylation (MsCl, Et_3N, CH_2Cl_2, 0°C, 97%), (ii) reaction with sodium azide (DMF, 90°C, (5), 57%) and (iii) reduction[6] (Ph_3P, THF-H_2O, 7:1, r.t., 98%). The amine (6) was hydrolyzed with acid (1 N HCl, THF, reflux, 1h) and then acetylated to give triacetylsphingosine (7) in 43% yield. The stereochemistry of (7) was confirmed by comparison with reported physical data [m.p. 104.6-106°C, $[\alpha]_D^{22}$ -21.6° (c = 0.88, AcOH); lit.[4] m.p. 106-107°C, $[\alpha]_D^{21}$ -22.3° (c = 2, AcOH)]. Acylation of (6) with p-nitrophenylpalmitate (py, r.t.) gave (8) in 98% yield. The ^1H NMR spectrum of (8) showed an equatorial arrangement of substituents on the 1,3-dioxacyclohexane ring (H-3, δ 4.20, t, $J_{2,3} = J_{3,4}$ = 8 Hz). Catalytic hydrogenation of (8) using 5% rhodium on alumina at room temperature under atmospheric pressure gave (9) in 93% yield.[7] Having obtained the requisite precursor, we turned our attention to the construction of the sulfonic acid moiety. One of the most useful synthetic reactions for introducing a bromine atom at C-1 is the Hanessian-Hullar reaction.[8] Treatment of the acetal (9) with freshly recrystallized N-bromosuccinimide in refluxing carbon tetrachloride in the presence of solid barium carbonate gave bromo benzoate (10) as an oil in 72% yield. Various attempts to convert the bromide (10) into mercaptane were unsuccessful. To this end, the bromide (10) was directly converted to sulfonic acid (11)[9] in 59% yield by sodium sulfite under a phase-transfer condition (n-Bu_4NBr, $CHCl_3$-H_2O, reflux, 4 days) followed by acidification. Base hydrolysis (1% NaOH in MeOH, r.t.) of (11) gave the dihydro-DCS (2)[10] in 68% yield (m.p. 104.5-106.2°C, $[\alpha]_D^{28}$ -3.13°, c = 0.16, $CHCl_3$-MeOH 9:1, FAB MS (matrix: glycerol+thioglycerol): m/z 604 $[M+1]^+$). The sulfonic acid was characterized as its ammonium salt, obtained by ammonium hydroxide in methanol, (12) [m.p. 171-173°C, FAB MS (matrix: glycerol+thioglycerol): m/z 621 $[M+1]^+$, 604 $[M-17]^+$; TLC: SiO_2, $CHCl_3$-MeOH-H_2O 65:25:3, R_f 0.35), which was identical with the natural dihydro-DCS (m.p. 169.5-174.3°C; TLC: SiO_2, $CHCl_3$-MeOH-H_2O 65:25:3, R_f 0.52, 0.35 (major), 0.02).

Preparation of (1c) via (13) by an essentially similar reaction sequence was unsuccessful. That is, the reaction of (13) with sodium sulfite was very slow and also the double bond was partially reduced under the reaction conditions to give a complex mixture. Further efforts are being directed toward the synthesis of (1c).

Acknowledgement

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References and Notes

1. R. Anderson, M. Kates and B.E. Volcani, Biochem. et Biophys. Acta, 528, 89 (1978).
2. Preparation of saturated-DCS (2): Total lipids of diatom cells (freeze-dried, 5 g) were extracted with $CHCl_3$-MeOH-H_2O (1:2:0.8, 190 ml) as described in ref. 1. The lipids obtained (140 mg) were then deacylated in 10 ml of 0.1 N NaOH in MeOH-$CHCl_3$ (4:1) at r.t. for 40 min; $CHCl_3$ (6 ml) and 1 N HCl (7.2 ml) were added, the biphasic mixture was centrifuged and the lower layer was removed, diluted with benzene and made alkaline with 1.5 N NH_4OH in MeOH and concentrated to a small volume (0.5 ml) under a stream of N_2. The ammonium salts of the acidic lipids (DCS and sterol sulfate) were then precipitated by tenfold dilution with acetone at 4°C. The precipitate was centrifuged, washed with 1 ml of cold acetone and dried in vacuum; a second crop was obtained from the combined acetone supernatants.

   The combined crops were then treated with 2 ml of 0.005 M HCl in THF for 3 h at r.t. Chloroform-methanol (1:1, 10 ml) and 0.2 N aqueous HCl (4.5 ml) were added, the biphasic system was centrifuged and the lower $CHCl_3$ phase was made alkaline with 1.5 N methanolic NH_4OH, diluted with benzene and brought to dryness in a stream of N_2. The residue was precipitated from $CHCl_3$-MeOH (1:1, 0.5 ml) by tenfold dilution with acetone at 0°C. The acetone insoluble material in methanol solution was hydrogenated with PtO_2 catalyst by bubbling H_2 for 15 min. The catalyst was removed by centrifugation, washed with MeOH-$CHCl_3$ (2:1) and the combined supernatants were diluted with $CHCl_3$ and 0.1 N HCl to form two phases. The lower chloroform phase was made alkaline with 1.5 N NH_4OH in methanol and brought to dryness under a stream of N_2. The residue was dissolved in $CHCl_3$-MeOH (1:1), cleared by centrifugation and the supernatant was brought to dryness under a stream of N_2; yield of hydrogenated-DCS, 2.5 mg; TLC R_f in $CHCl_3$-MeOH-NH_4OH (65:35:5), 0.73 (slight contamination with sterol sulfate, R_f 0.65); FAB-MS (matrix: glycerol+thioglycerol): m/z 621 $[M+1]^+$, 604 $[M-17]^+$.
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4. R.R. Schmidt and P. Zimmermann, Tetr. Lett., 27, 481 (1986).
5. Koike's report in ref. 3.
6. S. Pilard and M. Vaultier, Tetr. Lett., 25, 1555 (1984); J.R. Falck, S. Manna, J. Viala, A.K. Siddhanta, C.A. Moustakis and J. Capdevils, Tetr. Lett., 26, 2287 (1985).
7. When the double bond of (4) was reduced first, the dihydro derivative of the corresponding amine (6) could not be acylated even under forcing conditions probably due to steric hindrance by a "floppy" large alkyl group.
8. S. Hanessian and N.R. Plessas, J. Org. Chem., 34, 1035 (1969); T.L. Hulllar and S.B. Siskin, J. Org. Chem., 35, 225 (1970).
9. Physical data of (11): IR($CHCl_3$); 3245, 1720 and 1270 cm^{-1}, ^1H NMR($CDCl_3$, 200 MHz); 3.98 (2H, d, J = 8.3 Hz, H-1), 4.32 (1H, q, J = 8.2 Hz, H-2), 4.80 (1H, dt, J = 2.8 and 8.3 Hz, H-3) and 5.36 ppm (1H, br, NH).
10. Physical data of (2): IR(Nujol); 3300, 1260 and 1060 cm^{-1}, ^1H NMR($CDCl_3$, 270 MHz); 3.51-3.59 (4H, m, H-1, H-2, H-3), 4.32 (1H, m, NH) and 6.80 ppm (1H, br, SO_3H).

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