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SYNTHESIS OF PHOSPHONOSPHINGOGLYCOLIPID FOUND IN MARINE SNAIL TURBO CORNUTUS

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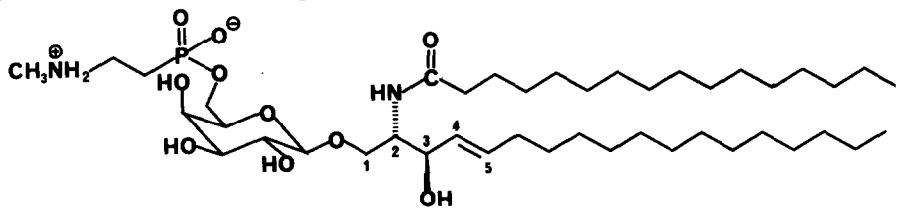
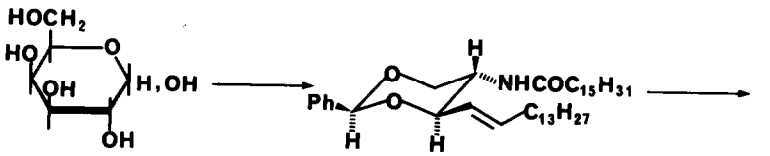
Abstract: The phosphonosphingoglycolipid (1) found in marine snail Turbo cornutus is synthesized from galactose as a chiral precursor via condensation of cerebroside (7) with protected phosphonic acid using DEC as the key step.

Recently many phosphonosphingoglycolipids have been isolated from the tissues of marine Mollusca and marine Protostomia.[1] Although their biological functions are not clear, but these compounds probably play important roles as receptors or transmitters of information. Hayashi and his colleagues isolated new phosphonosphingoglycolipids from the muscle tissues of the marine snail Turbo cornutus. For one of the simplest components, they proposed structure (1) by means of degradative work and spectroscopic analysis.[2] The first synthesis of (1) is reported herein.

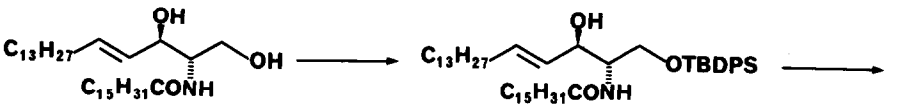


(1)

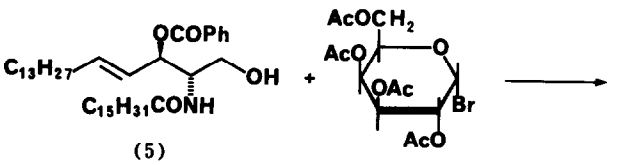
In a previous paper,[3] we showed that the protected ceramide (2) could be prepared efficiently from galactose using modified Schmidt's procedure.[4] Hydrolysis of the acetal (2) with acid (2N HCl, THF, reflux, 1h, 72%) gave ceramide (3) [m.p. 95-96°C, $[\alpha]_D^{28}$ -5.8° (c = 0.98, $CHCl_3$-MeOH 9:1), FAB MS; m/z 538 $(M+1)^+$]. Glycosidation of the ceramide at the C-1 hydroxy group succeeded only when the allylic alcohol was protected; this agreed with the findings of Thornton.[5] The protected alcohol (5) was obtained by the following reaction sequence: 1. Silylation (t-$BuPh_2SiCl$, imidazole, DMF, 60°C, 12h, (4), 67%), 2. benzoylation (PhCOCl, pyridine, r.t., 0.5h, 88%) and 3. desilylation (n-Bu_4NF, THF, r.t., 1h, 90%). Glycosidation with α-D-bromotetraacetylgalactose and (5) using Thornton's procedure[5] ($Hg(CN)_2$, CH_3NO_2, 80°C, 1.5h, 83%) gave a mixture of three components, one of which was probably an orthoester as



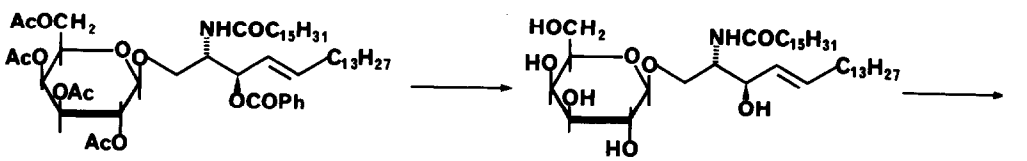
(2)



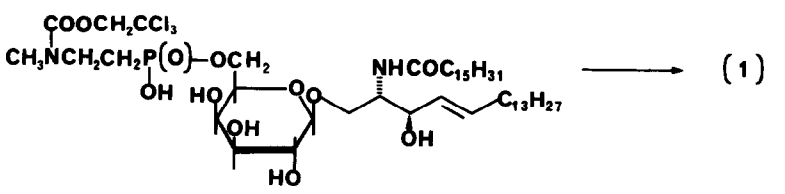
(3) (4)



(5)



(6) (7)



(8) (1)

Scheme 1

suggested by Ogawa.[6] Thus the mixture was treated with trimethylsilyltriflate[6] ($ClCH_2CH_2Cl$, 4A molecular sieves, 0°C, 1h), and the desired 1-O-β-D-tetraacetylgalactosylceramide (6) was obtained in 42% yield from (5). In order to obtain (6) in pure form, we explored the Lubineau procedure.[7] Treatment of (5) with α-D-bromotetraacetylgalactose, stannous triflate and 1,1,3,3-tetramethylurea as a base in the presence of 4A molecular sieves (r.t., 12h) gave pure (6) [^{1}H NMR: $CDCl_3$, 270 MHz: 1.99, 2.06, 2.07, 2.16 (4OAc), 3.65 (t, J = 6.2 Hz, H-1), 3.86 (dt, J = 1.0 and 6.2 Hz, H-2), 4.60 (d, J = 8.0 Hz, H-1'), 5.29 (dd, J = 7.8 and 15.1 Hz, H-4), ca. 5.3 (m, H-3) and 5.75 ppm (dt, J = 7.5 and 15.1 Hz, H-5), FAB MS: m/z 972 $(M+1)^+$] in 47% yield.

The synthesis of the protected 2-methylaminoethylphosphonic acid (9) was achieved in four steps using the method of Isbell[8] (Scheme II).

$$(EtO)_3P + BrCH_2CH_2Br \xrightarrow[79\%]{160^\circ C} (EtO)_2P(O)CH_2CH_2Br \xrightarrow[0^\circ C \text{ to r.t., } 94\%]{CH_3NH_2/Et_2O}$$

$$(EtO)_2P(O)CH_2CH_2NHCH_3 \xrightarrow[\text{Amberlite IR-120}]{\text{HBr/reflux;}} (HO)_2P(O)CH_2CH_2NHCH_3 \xrightarrow[\text{NaOH}]{ClCO_2CH_2CCl_3}$$

$$(HO)_2P(O)CH_2CH_2N(CH_3)COOCH_2CCl_3$$

(9)

Scheme II

After many unsuccessful attempts, we found that condensation of an alcohol with (9) could be carried out most effectively using dicyclohexylcarbodiimide (DCC) as a dehydrating agent. Furthermore, model studies[9] have shown that this phosphonation proceeds selectively at the primary hydroxy group of galactose moiety without special protection of other hydroxy groups. Treatment of (6) with sodium methoxide in methanol (r.t., 30min, 95%) gave pentaol (7) (m.p. 124.5-125.8°C). Ultrasound-assisted coupling of (7) and (9) was accomplished using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (DEC)[10] and pyridine (60°C, 22h, 72%) to give (8) [FAB MS: m/z 997 $(M+1)^+$]. In the absence of ultrasound, such a coupling did not occur. Deprotection of (8) with zinc and 90% aq. acetic acid (r.t., 5h) followed by chromatography on Iatrobeads®[11] ($CHCl_3$-MeOH-H_2O 9:1:0 then 65:25:4 as eluent) gave (1) as fine needles (m.p. 154.5-155.9°C from acetone) in 81% yield, which was identical with the natural lipids. [FAB MS: m/z 821 $(M+1)^+$, 520 ($C_{34}H_{66}O_2N^+$: ceramide), and 140 ($C_3H_{11}NO_3P^+$: methylaminoethylphosphonic acid moiety); $[\alpha]_D^{19}$ -2.5° (c = 0.16, $CHCl_3$-MeOH 9:1); TLC (silica gel 60 F_{254}: $CHCl_3$-MeOH-28%NH_4OH 56:38:10) R_f 0.23; natural lipids, m.p. 150.5-155.5°C, R_f 0.21].

Acknowledgement

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References and Notes

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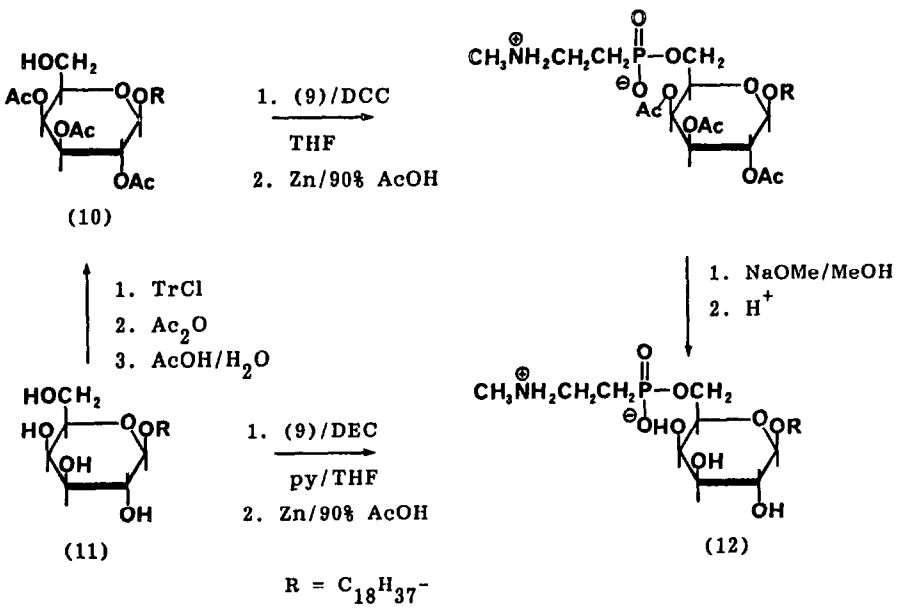
9. The same product (12) was obtained from either (10) or (11) (Scheme 3).



Scheme 3

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