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AN APPROACH TOWARDS THE FORMATION OF AN ESTER BOND BETWEEN THE PRIMARY HYDROXYL OF A β-D-GALACTOPYRANOSIDE AND 2-AMINOETHYLPHOSPHONIC ACID AND ITS N-METHYL SUBSTITUTED DERIVATIVES

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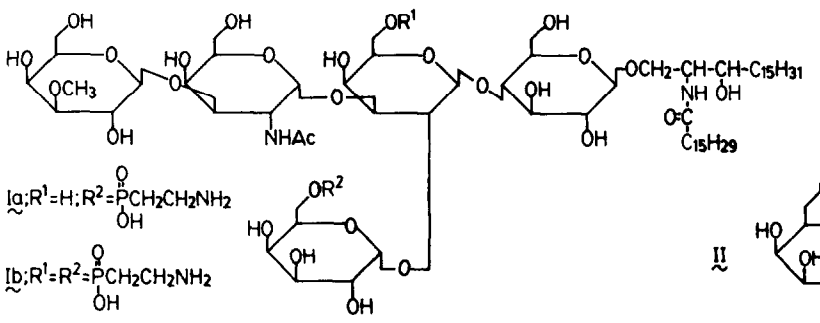
Abstract: An expeditious method for the preparation of the phosphonylating reagent 2-bromoethylphosphonic acid is presented. The latter compound as well as salicylchlorophosphite proved to be suitable for the synthesis of methyl O-6-(2'-aminoethylphosphonyl)-β-D-galactopyranoside and N-mono- or dimethylated derivatives thereof.

It is well-established now[1] that 2-aminoethylphosphonic acid[2] (ciliatine) is present mostly as part of a glycerolipid molecule, a phosphonic analogue[3] of phosphatidylethanolamine. The latter so called phosphonolipids[4] are extremely resistant towards enzymatic hydrolysis[5]. For instance, replacement of a phosphate ester by phosphonate at position *sn*-3 inhibits the action of phospholipase C[6]. It has also been established[7] that β-D-galactopyranosyl units esterified at O-6 with 2-aminoethylphosphonic acid occur in the D-galactan of albumen glands of the snail *Megalobulimus paranaguensis*. Recently, the complete structure of ceramide mono[8]- and bis[9](2-aminoethylphosphono)-pentaosides (i.e. Ia, b), isolated from the skin of *Aplusia kurolai*,were proposed.

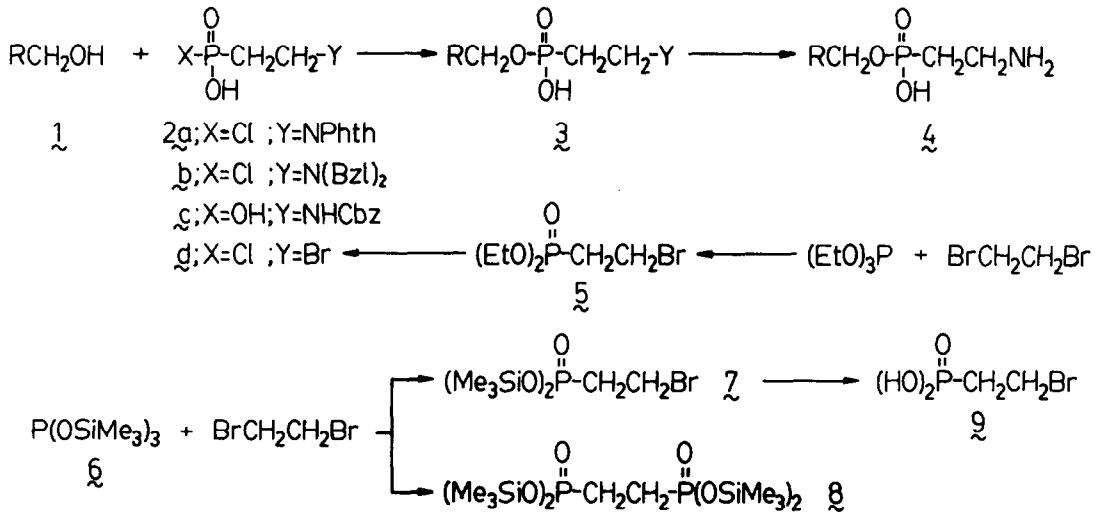


As part of a programme directed towards the preparation of the phosphonoglycosphingolipids Ia, b and derivatives thereof, we studied in detail the formation of an ester linkage between 2-aminoethylphosphonic acid and O-6 of a properly protected D-galactopyranoside.

We now report a convenient method for the preparation of the important phosphonylating reagent 2-bromoethylphosphonic acid (9, in Scheme 1), and the use of the phosphitylating reagent salicylchlorophosphite (12, in Scheme 2) for the introduction of the 2-aminoethylphosphonic acid function.

The development of phosphonylating reagents suitable for the synthesis of 2-aminoethylphosphonolipids is mainly due to the pioneering work[10] of Baer and Kosolapoff. The different kind of reagents and their use in the preparation of 2-aminoethylphosphonate esters is outlined in Scheme 1. For instance, phosphonylation of 1 with reagent 2a[4] affords 3 (Y=NPhth), the phthaloyl group of which is removed by hydrazinolysis to give 4. Similarly, 2b[11] will

Scheme 1; Baer-Kosolapoff approach

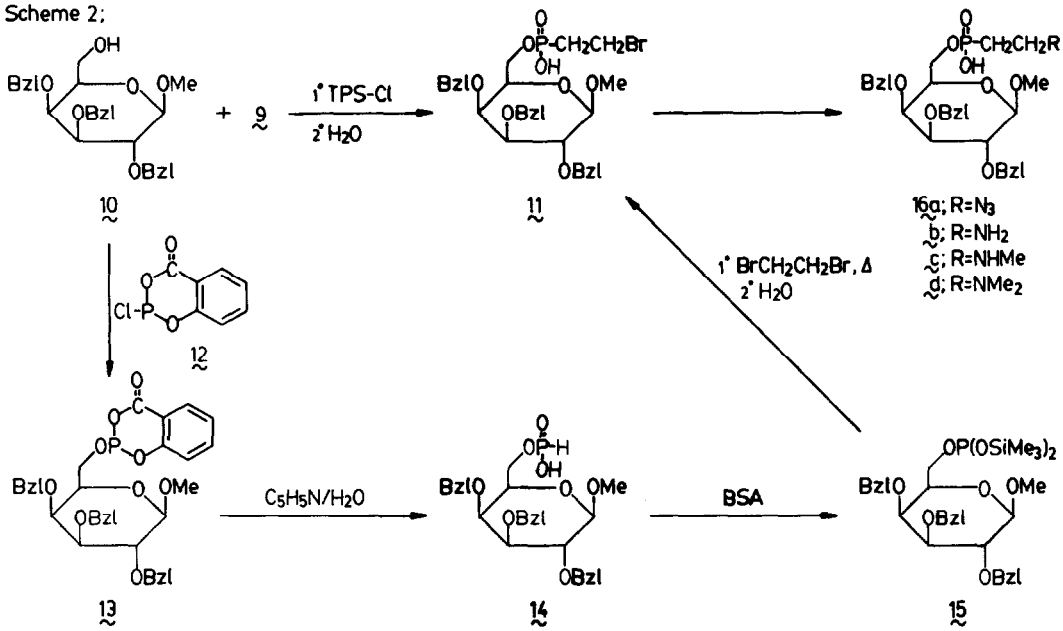


furnish 3 [Y=N(Bzl)$_2$] from which the benzyl protecting groups are removed by hydrogenolysis. In the case of 2c[12], formation of 3 (Y=NHCbz) is accomplished using an activating reagent. Hydrogenolytic cleavage of the benzyloxycarbonyl group then yields 4. On the other hand, reagent 2d[13], obtained by treating 9 with PCl_5, has a wider range of application than reagents 2a-c. The versatility of 9 or 3 (Y=Br) is due to the fact that the bromide ion can be substituted by ammonia[14] and amines[15]. For example, 2b is obtained by treating 9 with dibenzylamine followed by chlorination with PCl_5. Further, replacement with methylamine would give access to an N-methylaminoethylphosphonic acid function present[15] in the viscera of *Turbo cornutus* (see II). The preparation of 9 is, however, rather tedious and time-consuming. The first step, as devised by Kosolapoff[16], involves an Arbuzov reaction of triethyl phosphite with ethylene dibromide to afford 5 (see Scheme 1). Acid hydrolysis of 5, to give 9, is then executed[13] with concentrated hydrobromic acid (20 h, 95°C). McKenna et al.[17] found that the harsh hydrolysis conditions could be circumvented by converting 5 with trimethylsilyl bromide into the corresponding bis(trimethylsilyl)ester 7, which can be smoothly hydrolysed with water[18]. An alternative approach to 9 would be the use of tris(trimethylsilyl)phosphite[19] in the Arbuzov reaction. Thus 6 (0.1 mol), prepared according to Hata et al.[19c], was treated, under a stream of nitrogen, with excess ethylene dibromide (0.46 mol) for 8 h at 125°C. Distillation of the reaction mixture afforded 7[20] (b.p. 102°C/0.2 mm Hg, ^{31}P-NMR, δp 6.92 ppm, yield 84%) not contaminated with the possible[21] by-product 8. Hydrolysis of the silyl esters in 7 was easily accomplished with methanol-water (9:1, v/v). After 90 min at 20°C, the solvents were removed and the solid mass was recrystallized from $CHCl_3$ to give 9[20] (m.p. 94-95°C; lit.[13], 93-95°C, ^{31}P-NMR, δp 30.46 ppm) in a yield of 90%.

The use of 9 in the preparation of the D-galactopyranoside phosphonate derivative 11 is illustrated in Scheme 2. To a cooled (0°C) solution of 10 (5 mmol) and 9 (7.5 mmol) in dry pyridine (25 ml) was added 2,4,6-tri-isopropylbenzenesulfonyl chloride (15 mmol). After 4 h, water was added, and the mixture was poured into aqueous triethylammonium bicarbonate (TEAB, 1 M, 15 ml). The solution was extracted with CH_2Cl_2, and the combined organic fractions were dried and evaporated. Crude 11 thus obtained was purified (Sephadex LH-20) to give homogeneous[20] 11

(TEAB-salt, ^{31}P-NMR: one resonance at 18.01 ppm) in a yield of 66%.

Scheme 2:



An alternative approach, which is based on the recently by us introduced[22] phosphitylating reagent salicylchlorophosphite 12, is illustrated in Scheme 2. To a solution of 10 (5 mmol) in dioxane (15 ml) and pyridine (5 ml) was added 12 (5.5 mmol). ^{31}P-NMR spectroscopy revealed rapid formation of intermediate phosphite triester 13 (^{31}P-NMR: one resonance at 126.92 ppm). After 15 min, the reaction mixture was hydrolysed with water (1 ml). Further work-up and purification, as mentioned before, gave the homogeneous[20] TEAB-salt of 14 (^{31}P-NMR: one resonance at 3.35 ppm, J_{PH}≈615 Hz) in a yield of 90%. Silylation of 14 (5 mmol) in acetonitrile (25 ml) was effected with N,O-bis(trimethylsilyl)acetamide[23] (3.09 ml, 12.5 mmol) in the presence of triethylamine (1.74 ml). After 15 min at 20°C the mixture was concentrated and coevaporated

15 thus obtained showed the presence of one resonance at 120.03 ppm. Compound 15 was then heated with ethylene dibromide (25 ml) for 4 h at 100°C. Usual work-up and purification afforded homogeneous 11 (yield 82%), which was in every aspect - ^{31}P- and ^{13}C-NMR spectroscopy - identical with 11 obtained by the direct approach. Substitution of the bromide ion in 11 could be accomplished by heating the compound (1.36 mmol) in DMF (20 ml) with lithium azide (13.5 mmol) for 16 h at 100°C. Work-up and purification furnished homogeneous[20] 16a [^{31}P-NMR: one resonance at 18.98 ppm; IR (neat) ν 2100 cm^{-1}] in a yield of 92%. The azide function in 16a was easily reduced with H_2S in pyridine-water[24], to afford, after usual work-up, the 2-aminoethylphosphonate 16b[20] (δp 20.07 ppm) in an excellent yield. The latter compound was also obtained by ammination of 11 according to the procedure of Eibl et al.[25]. Similarly, the mono- and dimethylamino derivatives 16c[20] (δp 17.22 ppm) and 16d[20] (δp 17.98 ppm) were isolated in good yields upon reaction of 11 in acetontrile (14 ml) with methylamine (10 eq.) and dimethylamine (10 eq.), respectively, for 16 h at 20°C.

We believe, that the two approaches described in this paper may be of great value in the ultimate synthesis of the complex oligosaccharides Ia, b and derivatives thereof. Further,

the relatively low yield we observed in preparing 11, via the 2-bromoethylphosphonic acid (9) approach, may be improved by converting the now easily accessible 2-bromoethylphosphonyl dichloride[26] into reagents activated with 1-hydroxybenzotriazole derivatives[27]. On the other hand, the salicylchlorophosphite approach gives, apart from 11, an easy access to the 1-H-phosphonate 14 and the bis(trimethylsilyl)phosphite 15. The latter can be oxidised[23c] or sulfurised[23b] to afford 6-O-phosphate or thiophosphate derivatives of 10, respectively.

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20. Relevant analytical data are given below.
^{13}C-NMR data (δ-values): 7, 0.5 ($Si(\underline{C}H_3)_3$), 24.0 ($\underline{C}H_2Br$), 33.1 ($\underline{C}H_2P$, J_{CP}=141 Hz); 9, 24.2 ($\underline{C}H_2Br$), 31.9 ($\underline{C}H_2P$, J_{CP}=132 Hz); 11, 27.7 ($\underline{C}H_2Br$), 32.4 ($\underline{C}H_2P$, J_{CP}=127 Hz), 62.4 (br, C_6), 73.4 (br, C_5), 104,5 (C_1); 14, 61.5 (br, C_6), 73.2 (br, C_5), 104.5 (C_1); 16a, 26.8 ($\underline{C}H_2P$, J_{CP}=132 Hz), 47.0 ($\underline{C}H_2N_3$), 62.4 (br, C_6), 73.5 (br, C_5), 104.8 (C_1); 16b, 24.0 ($\underline{C}H_2P$, J_{CP}= 132 Hz), 35.2 ($\underline{C}H_2NH_2$), 62.8 (br, C_6), 73.6 (br, C_5), 104.5 (C_1); 16c, 21.1 ($\underline{C}H_2P$, J_{CP}=133 Hz), 38.8 ($NH\underline{C}H_3$), 53.2 ($\underline{C}H_2NHMe$), 63.6 (br, C_6), 73.7 (br, C_5), 104.7 (C_1); 16d, 22.4 ($\underline{C}H_2P$, J_{CP}=129 Hz), 42.0 ($N(\underline{C}H_3)_2$), 53.4 ($\underline{C}H_2NMe_2$), 62.4 (br, C_6), 73.6 (br, C_5), 104.7 (C_1). Mass spectroscopy of compound 7; $C_8H_{22}BrO_3PSi_2$, $M^{+\cdot}$=332 and 334.
Elemental analyses of compounds 11, 14 and 16a-d (TEA-salts): 11, Calc. P 4.20, Found P 4.25; 14, Calc. P 4.92, Found P 4.80; 16a, Calc. C 61.88, H 7.36, N 8.02, Found C 61.72, H 7.32, N 7.99; 16b, Calc. C 64.27, H 7.94, N 4.16, Found C 64.32, H 7.89, N 4.12; 16c, Calc. C 64.70, H 8.07, N 4.08, Found C 64.56, H 8.12, N 4.10; 16d, Calc. C 65.12, H 8.20, N 4.00, Found C 65.30, H 8.25, N 3.95.
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