Tetrahedron Letters,Vol.28,No.11,pp 1163-1164,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHESIS OF ALLYLIC PHOSPHONATES OF BIOLOGICAL INTEREST

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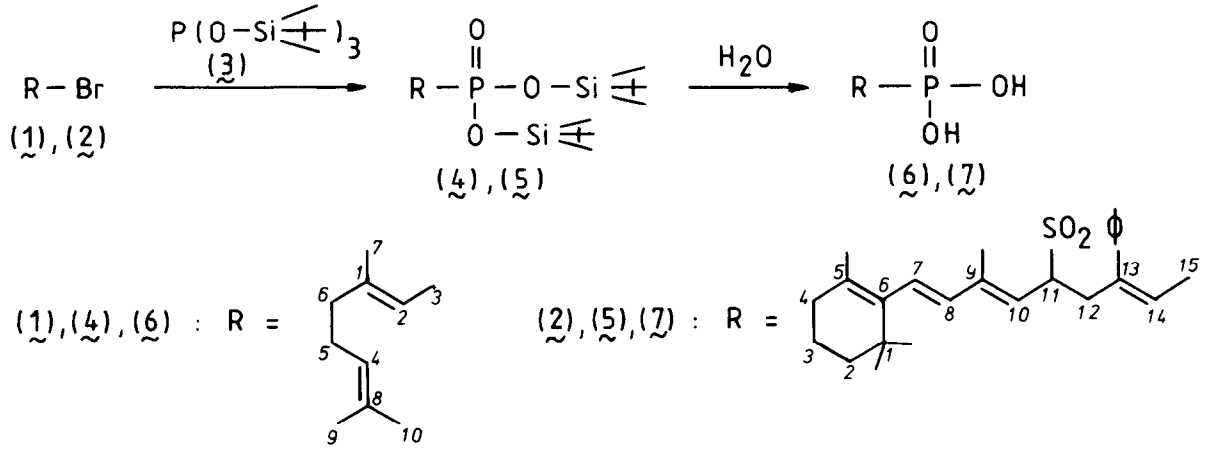
Summary. *A novel route to the synthesis of allylic phosphonates of biological interest is described.*

Tris (trimethylsilyl) phosphite[1,2] $P(OSiMe_3)_3$ has not been used extensively in the Michaëlis-Arbusov reaction. However, use of this compound has allowed us to prepare geranyl phosphonate (6) rapidly and in high yield. The latter is wellknown for its inhibitory action in liver prenyltransferase[3]. This method compares favorably with the dealkylation of dialkyl-esters of phosphonic acid with trimethylbromosilane as developed by Mc Kenna[4].

Alkylbistrimethylsilyl phosphonate $R\text{-}PO(O\text{-}Si\ Me_3)_2$ is very sensitive to moisture[5]. When the molecular weight of R is high, these compounds cannot be purified by distillation since they hydrolyse to mixtures from which it is difficult to isolate the desired product.

To obviate this difficulty we have prepared tris(t-butyldimethylsilyl)phosphite (3). This new phosphite and its Arbusov reaction products are less sensitive to moisture than the corresponding trimethylsilyl derivatives.



Geranyl bis(t-butyldimethylsilyl) phosphonate can be purified by silica gel column chromatography with anhydrous solvents and subsequently hydrolysed with H_2O at room temperature.

We applied this method to the synthesis of a phosphonate analog of retinyl phosphate, a key factor in the biosynthesis of the glycan part of certain membrane glycoconjugates[6].

Geranyl bromide (1) was obtained in nearly quantitative yield by action of PBr_3 on

geraniol. Preparation of alkylbromide (2) was accomplished by modification of a vitamine A synthesis[7].

Tris(t-Butyldimethylsilyl)phosphite (3) (B_p = 82°C/0.2 mm Hg ; ^{31}P NMR : 113.96 p.p.m.) was prepared in the same manner as tris(trimethylsilyl) phosphite[8] replacing trimethylchlorosilane by t-butyldimethylchlorosilane. The Arbusov reaction was carried out, without solvent, using two equivalents of phosphite (3), progressively heating the mixture to 90°C over 1 h. This temperature was then maintained for 1 h. Silylating phosphonates (4)[9] and (5)[9] were obtained in 80 % yield after chromatographic purification. This yield is equivalent to that found after distillation of geranyl bis(trimethylsilyl) phosphonate (B_p = 133-135°C C/0.2 mm Hg). The hydrolysis of compounds (4) and (5) was carried out in 50 % aqueous methanol at room temperature affording the free phosphonates (6)[9] and (7)[9] in quantitative yield.

Utilization of this new phosphite (3) allows chromatographic purification of the Arbusov reaction products which in turn can be cleanly converted to the corresponding phosphonate esters. Access to phosphonate esters of biological interest is therefore improved.

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(9) *Geranyl,bis(t-butyldimethylsilyl)phosphonate* (4), PMR (90 MHz, $CDCl_3$, δ) : 5.20(m, 2H, H-2 and H-4), 2.45 (q,2H,H-3), 2.01(m, 4H, H-5 and H-6), 1.52 (s,6H, H-9 and H-10), 1.65 (s,3H, H-7), 0.88 (s, 18H, t-butyl-Si), 0.22 (s, 12H, CH_3-Si) ; MS m/z(%) : 446 (M^+,30), 431(20), 389(100), 377(41), 321(71), 309(10), 268(16), 237(8), 135(32) ; ^{31}P NMR(200 MHz, $CDCl_3$,S) : 10.60. *Nonatrienyl phosphonate* (5), PMR (90 MHz, $CDCl_3$, S) : 7.67 (m, 5H, $SO_2\phi$),6.01 (s, 2H, H-7 and H-8), 5.22 (m, 2H, H-10 and H-14), 4.06 (m, 1H, H-11), 2.57 (m,4H, H-12 and H-15), 2.02 (m, 2H, H-4), 1.69 (s, 6H, CH_3-C_9 and C_{10}), 1.29 (s, 3H, CH_3-C_5), 0.98 (s, 6H, CH_3-C1), 0.90 (s, 18H, t-butyl-Si), 0.25 (s, 12H,CH_3-Si). MS, FAB (Pos.) $M+H^+$: 721. ^{31}P NMR (200 MHz, $CDCl_3$, δ) : 9.35. *Geranyl phosphonate* (6), PMR (90 MHz, $CDCl_3$, δ) : 8.02 (s broad, 2H, O-H), 5.07 (m, 2H, H-2 and H-4), 2.60 and 2.25 (2d, 2H, H-3), 2.07 (m, 4H, H-5 and H-6), 1.67 (s, 6H, H-9 and H-10), 1.57 (s, 3H, H-7). MS, FAB (Pos.) $M+H^+$: 219. ^{31}P NMR (200 MHz, $CDCl_3$, δ) : 25,99. *Phosphonate* (7), PMR (90 MHz, $CDCl_3$, δ) : 7.55 (m, 5H, SO_2-ϕ), 6.5 (s broad, 2H, O-H), 5.89 (s, 2H, H-7 and H-8), 5.35 (t, 1H, H-14), 5.06 (d, 1H, H-10), 4.32 (m, 1H, H-11), 3.15-1.8 (m, 6H, H-12, H-15 and H-4), 1.35 (s, 6H, H-9 and H-13), 1.25 (s, 3H, CH_3-C_5), 0.96 (s, 6H, CH_3-C1). MS, FAB (Pos.) $M+H^+$: 493. ^{31}P NMR (200 MHz, $CDCl_3$, δ) : 24.63.

(Received in France 6 October 1986)