

Total Synthesis of the Potent Mutagen (*S*)-3-(Dodeca-1,3,5,7,9-pentaenyloxy)propane-1,2-diol

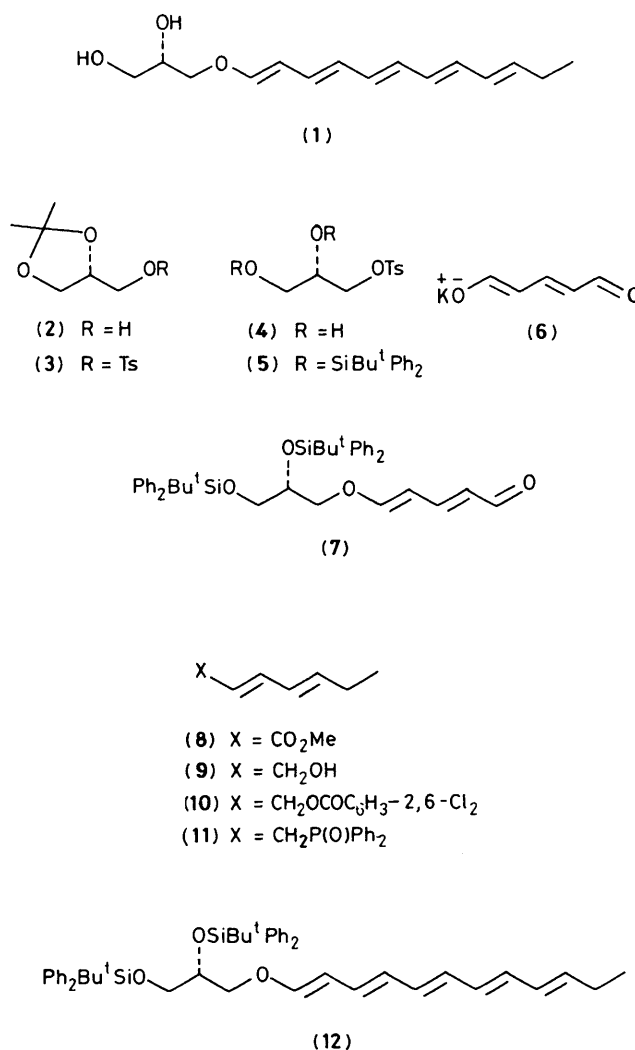
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A total synthesis of the mutagenic (*S*)-3-(dodeca-1,3,5,7,9-pentaenyloxy)propane-1,2-diol (**1**) from (*R*)-glycerol acetone (2), potassium glutaconate (**6**), and the diphenylphosphine oxide (**11**) is reported.

Structure (**1**) [(*S*)-3-(dodeca-1,3,5,7,9-pentaenyloxy)propane-1,2-diol] has recently been assigned to a potent mutagenic agent isolated from human faeces.^{1,2} The low natural abundance of this rather unstable biomolecule coupled with the need for further biological investigations to elucidate its possible role in colon cancer etiology dictated a synthesis. We now report a short and convenient total synthesis of (**1**) based on a highly convergent scheme.

(*R*)-Glycerol acetone (**2**)³ was tosylated (TsCl–pyridine,† 91%) and deprotected (10% aq. HCl, acetone, 75 °C, 80%) to afford the diol (**4**) via compound (**3**).‡ Silylation of (**4**) (Ph₂Bu^tSiCl–imidazole, DMF,† 94%) followed by displacement of the tosylate group in (**5**) by potassium glutaconate⁴ (**6**) (excess, DMF, 75 °C) furnished the dienol aldehyde derivative (**7**) [40%, ¹H n.m.r., CDCl₃, 250 MHz, δ 9.43 (1H, d, *J* 8.5 Hz, CHO), 7.25–7.65 (20H, m, Ph), 6.95 (1H, dd, *J* 15.0 and 12.0 Hz, CH=CHCHO), 6.78 (1H, d, *J* 12.0 Hz, OCH=), 7.00 (1H, dd, *J* 15.0 and 8.5 Hz, =CHCHO), and 6.63 (1H, *J* 12.0 Hz, OCH=CH)] together with minor amounts of its *Z* enol isomer from which it was separated by flash silica column chromatography [(7): *R*_f 0.18; *Z*-isomer of (7): *R*_f 0.28, 30% ether in light petroleum]. The diphenylphosphine oxide (**11**) required for the completion of the polyene chain was constructed as follows. Condensation of propionaldehyde with the anion of trimethylphosphonocrotonate (LDA, THF,† –78 → 25 °C, 78%) afforded the ester (**8**) which was reduced (excess of DIBAL,† CH₂Cl₂, –78 °C, 84%) to give



† Abbreviations: Ts = *p*-MeC₆H₄SO₂; DMF = dimethylformamide; LDA = lithium di-isopropylamide; THF = tetrahydrofuran; DIBAL = di-isobutylaluminium hydride; DMAP = 4-*N,N*-dimethylaminopyridine.

‡ All new compounds exhibited satisfactory spectra and analytical data.

the alcohol (**9**), esterified (2,6-dichlorobenzoyl chloride, pyridine, DMAP⁺ catalyst, CH₂Cl₂, 90%) to provide (**10**), and treated with the anion of diphenylphosphine⁵ (BuⁿLi, THF, -78°C) to afford, after H₂O₂ work-up, the requisite (**11**) (82%) [*R*_f 0.28, 2% methanol in ether-silica; m.p. 101–103°C (ether in light petroleum); ¹H n.m.r., CDCl₃, 250 MHz δ 7.88–7.40 (10H, m, Ph), 6.14–5.84 (2H, m, olefinic), 5.68–5.43 (2H, m, olefinic), 3.15 (2H, dd, *J*, 16.0 and 8.0 Hz, CH₂P), 2.05 (2H, m, CH₂CH₃), and 0.98 (3H, t, *J* 7 Hz, CH₃)].

Reaction of aldehyde (**7**) with the anion of (**11**) (LDA, THF, -78°C) gave the corresponding hydroxyphosphine oxide adduct which was decomposed under basic conditions (KOBu^t, THF, 0°C), leading to the bis(*t*-butyldiphenylsilyl) ether (**12**) (55%), purified by flash silica column chromatography [*R*_f 0.43; 5% ether in light petroleum; ¹H n.m.r., CDCl₃, 250 MHz, δ: 7.20–7.70 (20H, m, Ph), 6.41 (1H, d, *J* 12.0 Hz, OCH=), 5.66–6.25 (8H, m, olefinic), 5.48 (1H, m, olefinic), 3.58–4.02 (5H, m, CH–O, CH₂O), 2.15 (2H, m, CH₂CH₃), 1.04 and 1.00 (each 9H, s, Bu^t), and 1.01 (3H, *J* 7.0 Hz, CH₃)]. Finally deprotection of (**12**) (Buⁿ₄NF, THF, 0 → 25°C) led to the labile (**1**) which was obtained after flash

silica column chromatography (*R*_f 0.29, 2% methanol in ether) as a mixture with its *Z* enol isomer as reported.^{1,2§}

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