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

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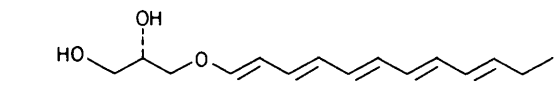
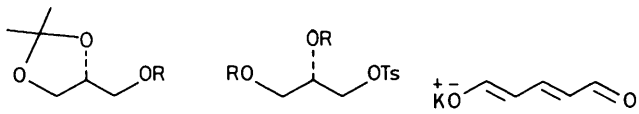
A total synthesis of the mutagenic (*S*)-3-(dodeca-1,3,5,7,9-pentaenyloxy)propane-1,2-diol (**1**) from (*R*)-glycerol acetonide (**2**), potassium glutaconate (**6**), and the diphenylphosphine oxide (**11**) is reported.

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 acetonide (**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**) (Ph_2-Bu^tSiCl–imidazole, DMF,† 94%) followed by displacement of the tosylate group in (**5**) by potassium glutaconate[4] (**6**) (excess, DMF, 75 °C) furnished the dienol aldehyde derivative (**7**) [40%, ^1H n.m.r., $CDCl_3$, 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, C*H*=CHCHO), 6.78 (1H, d, *J* 12.0 Hz, OCH=), 7.00 (1H, dd, *J* 15.0 and 8.5 Hz, =C*H*CHO), and 6.63 (1H, *J* 12.0 Hz, OCH=C*H*)] 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,† CH_2Cl_2, −78 °C, 84%) to give



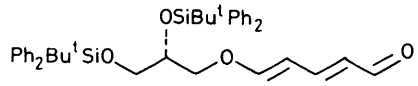
(**1**)



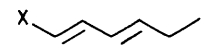
(**2**) R = H
(**3**) R = Ts

(**4**) R = H
(**5**) R = $SiBu^tPh_2$

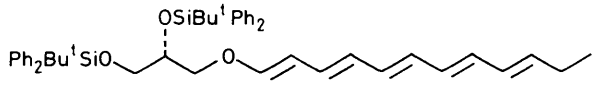
(**6**)



(**7**)



(**8**) X = CO_2Me
(**9**) X = CH_2OH
(**10**) X = $CH_2OCOC_6H_3$-2,6-Cl_2
(**11**) X = $CH_2P(O)Ph_2$



(**12**)

† Abbreviations: Ts = *p*-$MeC_6H_4SO_2$; 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, CH_2Cl_2, 90%) to provide (**10**), and treated with the anion of diphenylphosphine[5] (Bu^nLi, THF, −78 °C) to afford, after H_2O_2 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., $CDCl_3$, 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, CH_2P), 2.05 (2H, m, CH_2CH_3), and 0.98 (3H, t, *J* 7 Hz, CH_3)].

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., $CDCl_3$, 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, CH_2O), 2.15 (2H, m, CH_2CH_3), 1.04 and 1.00 (each 9H, s, Bu^t), and 1.01 (3H, *J* 7.0 Hz, CH_3)]. Finally deprotection of (**12**) ($Bu^n{}_4NF$, 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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