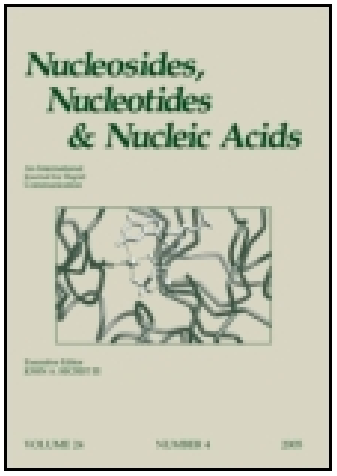

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Tetraethylene Glycol-Derived Spacer for Oligonucleotide Synthesis

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TETRAETHYLENE GLYCOL-DERIVED SPACER FOR OLIGONUCLEOTIDE SYNTHESIS

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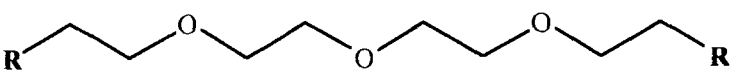
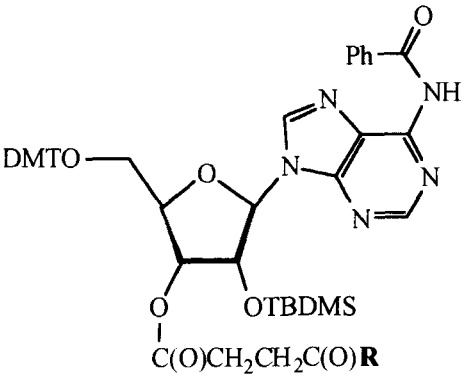
ABSTRACT. 3,6,9-Trioxaundecane-1,11-diisocyanate (**6**) was synthesised from tetraethylene glycol in 5 steps and 48 % overall yield. Spacer **6** was monofunctionalised with the fully protected adenosyl-3'-O-succinate derivative **7** and linked to aminomethyl polystyrene affording a solid support suitable for oligoribonucleotide synthesis (loading: ~20 μmol/g). The HPLC analysis of a crude oligoribonucleotide synthesis and the yield of the full-length product show that this spacer compares well to hexamethylene diamine.

The utility of hydrophilic spacers for the linkage of (bio)molecules to some solid support has gained importance with the wide-spread application of combinatorial chemistry. For the solid support synthesis of oligonucleotides a tetraethylene glycol spacer proved to be superior in terms of, both, coupling yields and homogeneity of the final product, when compared to several other tested spacer molecules of up to double its length. We envisaged combining the desirable properties of tetraethylene glycol-derived spacers, the optimal reactivity of a,w-diisocyanates, and the superiority of highly crosslinked (50 % divinyl benzene) aminomethyl polystyrene (H_2NCH_2-PS) over alkylamino controlled-pore glass (CPG), and synthesised 3,6,9-trioxaundecane-1,11-diisocyanate (**6**) from tetraethylene glycol (Scheme 1), coupled **6** – and, alternatively, hexamethylene diisocyanate (**8**) – to the fully protected adenosyl-3'-O-succinate derivative **7**, and linked **9** and **11**, respectively, to H_2NCH_2-PS (Scheme 2). Finally, both resins **10** and **12** were tested on the RNA synthesiser using commercial phosphoramidites and reagents (not shown). The isolated yield of an RNA decamer oligomerised on **10** was 43 % higher than that of the same sequence made in parallel on **12**.



R = OH (**1**) $\xrightarrow{a)}$ Br (**2**) $\xrightarrow{b)}$ N_3 (**3**) $\xrightarrow{c)}$ NH_2 (**4**) $\xrightarrow{d)}$ $NH_{1-0}(SiMe_3)_{1-2}$ (**5**) $\xrightarrow{e)}$ N=C=O (**6**)

SCHEME 1: a) Ph_3P, CBr_4, CH_3CN, 40°/18 h, MPLC: 85 %; b) NaN_3, DMF, 100°/100 h, MPLC: 93 %; c) H_2/Pd-$BaSO_4$, EtOH/H_2O 26:1, 1 atm/30 h, distill.: 93 %; d) Me_3SiNEt_2, $(NH_4)_2SO_4$, 85°/1.5 h→100°/24 h→ 150°/40 h; e) $(Cl_3CO)_2CO$, MgO, CH_2Cl_2, 25°/43 h, distill.: 65.4 % (**4**→**6**).



DMT: dimethoxytrityl
TBDMS: *tert*-butyldimethylsilyl

R = OH (**7**)

a) ↓ $-CO_2$

R = $NHCH_2CH_2O(CH_2CH_2O)_2CH_2CH_2NCO$ (**9**)

R = $NH(CH_2)_6NCO$ (**11**)

b) c) d) ↓

R = $NH(CH_2)_2O(CH_2CH_2O)_2(CH_2)_2NHC(O)NHCH_2$–PS (**10**)

R = $NH(CH_2)_6NHC(O)NHCH_2$–PS (**12**)

SCHEME 2: a) DMAP (1.0 equiv.), **6** or $OCN(CH_2)_6NCO$ (**8**) (1.0 equiv.), CH_2Cl_2, 15 min.; b) H_2NCH_2-PS (5 g/mmol **7**), Et(*i*-prop)$_2$N (1.0 equiv.), 48 h/CH_2Cl_2 (5 ml/g H_2NCH_2-PS), Et_2O (wash); c) H_2O/C_5H_5N (2:8), 2 h; d) Ac_2O/ Et_3N/N-methyl-imidazole/CH_2Cl_2 (1:1:0.3:6), 0.5 h.

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