chromatography on silica gel (elution with 40:1 benzene–ethyl acetate), gave a 54% yield of **12.**[10a,11a] Reaction of **12** with *m*-chloroperoxybenzoic acid (1 equiv, methylene chloride, −20–0 °C, 3 h) afforded the needed sulfoxide **13**[10a,11b] in 69% yield.

Heating of **2** and **13** (neat, 120 °C, 20 h) and treatment with 2.3% acetic acid in ethyl acetate followed by rapid chromatography on silica gel (elution with 4:1 benzene –ethyl acetate) gave a 41% crude yield of **14** contaminated with ~15% methoxy epimers **16** and **17.** In related cases,[8b] such contaminants can readily be removed by chromatography on silica gel. In the case at hand, dienone **14** is unstable to slow chromatography of the type required to separate it from **16** and **17.** Fortunately, homogeneous **14,**[10] mp 128–130 °C, was obtained by crystallization from ether but only in 17% yield. For our subsequent operations it was easier to use homogeneous **14** though dienols **15** and **18** (vide infra) could be obtained in pure form starting with crude **14.**

Treatment of **14** with 9-BBN[12] (3 equiv, THF, 0 °C to room temperature, 3 h) afforded a 3:2 ratio of **15:18.** These were separated by chromatography on silica gel. Each epimer was treated with 1.25 equiv of sodium hydroxide in aqueous methanol (14 h, room temperature). After lyophilization, the resultant disodium salts were dissolved in D_2O and their NMR spectra measured at 250 MHz.[13]

Starting with dienol **15**[10a,14] (R_f[15] 0.61, 9:1 chloroform–ethanol), there was thus obtained synthetic disodium prephenate **1a.** Its NMR spectrum[13,16] was identical with that of an authentic sample prepared from authentic barium prephenate by ion exchange (Dowex 50W-X8 Na^+ form).

From dienol **18**[10a,17] (R_f[15] 0.53, 9:1 chloroform–ethanol) there was obtained disodium epiprephenate **19a.** The NMR spectrum of **19a**[18] is similar in character but clearly different in detail (at 250 MHz) from that of **1a.**

We believe that this total synthesis will permit the introduction of isotopic perturbations into the prephenate system which will be of assistance in biosynthetic inquiries. Also, it would be of interest to ascertain, through analogue synthesis and biological examination, the effect of structural variations in the prephenate system on enzymic recognitions. In this connection, of course, the epiprephenate system will be of interest.

Finally, we would note that, with some yield improvements, total synthesis may well be the most effective method for obtaining prephenate salts.

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(9) For instance, treatment of either epimeric acetate of **7** with tosyl acid–acetone afforded an ~1:2 ratio methyl phenylpyruvate dimethyl acetal and the rearrangement product, methyl-2-carbomethoxyphenylpyruvate dimethyl acetal: unpublished results, T. Harayama, University of Pittsburgh.
(10) The structure of this compound is in accord with (a) its infrared and NMR spectral properties and (b) its combustion analysis within 0.4% of theory.
(11) (a) Vinyl sulfide **12** is a single compound but its stereochemistry is not known with certainty. (b) Sulfoxide **13** is obtained as a mixture of diastereomeric sulfoxides which was not separated.
(12) S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **42,** 1197 (1977).
(13) The water-soluble standard 3-trimethylsilyl-1-propanesulfonic acid was used. Data for **1a**[16] and **18a**[17] are reported in parts per million (δ) from the SiMe resonances.
(14) Dienol **15**: δ ($CDCl_3$) 2.07 (s, OH), 2.51 (s, CH_2), 3.49 (s, $ROCH_3$), 3.88 (s, RCO_2CH_3), 4.46 (ddt, J_1 = 3.9, J_2 = 3.8, J_3 = 1.0 Hz, C*H*OH), 5.71 (ddd, J_1 = 9.9, J_2 = 2.2, J_3 = 1.0 Hz, vinyl H at C_3 or C_5), 6.02 (ddd, J_1 = 9.9, J_2 = 2.2, J_3 = 1.0 Hz, vinyl H at C_5 or C_3), 6.18 (ddd, J_1 = 9.9, J_2 = 3.8, J_3 = 1.5 Hz, vinyl H at C_2 or C_6), 6.25 (ddd, J_1 = 9.9, J_2 = 3.9, J_3 = 1.5 Hz, vinyl H at C_6 or C_2) ppm; $\tilde{\nu}$($CHCl_3$) 3520, 1783, 1754 cm^{-1}.
(15) R_f values were determined on commercial (E. M. Merck) precoated silica gel (60F-254 TLC) plates.
(16) **1a:** δ^{13} (D_2O) 4.50 (tt, J_1 = 3.1, J_2 = 1.4 Hz, C*H*OH), 5.92 (dd, J_1 = 10.4, J_2 = 3.1 Hz, vinyl hydrogens at C_2 and C_6), 6.01 (dd, J_1 = 10.4, J_2 = 1.4 Hz, vinyl hydrogens at C_3 and C_5) ppm. The methylene protons at C_7 are exchanged in basic D_2O.
(17) **18:** δ ($CDCl_3$) 1.80 (br, s, OH), 2.53 (d, J = 14.2 Hz, H_A at C_7), 2.56 (d, J = 14.2 Hz, H_B at C_7), 3.48 (s, $ROCH_3$), 3.88 (s, RCO_2CH_3), 4.71 (ddt, J_1 = 3.0, J_2 = 2.7, J_3 = 1.9 Hz, C*H*OH), 5.64 (dt, J_1 = 9.9, J_2 = 1.9 Hz, vinyl H at C_3 or C_5), 5.97 (dt, J_1 = 9.9, J_2 = 1.9 Hz, vinyl H at C_5 or C_3), 6.09 (ddd, J_1 = 9.9 Hz, J_2 = 2.7 Hz, J_3 = 1.9 Hz, vinyl H at C_2 or C_6), 6.17 (ddd, J_1 = 9.9, J_2 = 3.0, J_3 = 1.9 Hz, vinyl H at C_6 or C_2) ppm; $\tilde{\nu}$($CHCl_3$) 3623, 3436, 1786, 1754 cm^{-1}.
(18) **19a:** δ^{13} (D_2O) 4.55 (tt, J_1 = 3.1, J_2 = 1.5 Hz, C*H*OH), 5.89 (dd, J_1 = 10.3, J_2 = 3.1 Hz, vinyl hydrogens at C_2 and C_6), 5.99 (dd, J = 10.3, 1.5 Hz, vinyl hydrogens at C_3 and C_5). The methylene protons at C_7 are exchanged in D_2O.

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Synthesis of Oligoribonucleotides

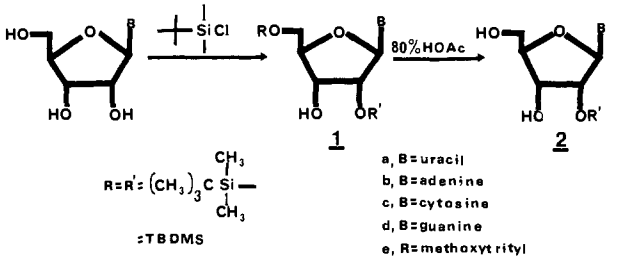
Sir:

During the past decade major advances in the synthesis of oligodeoxyribonucleosides have been made. The Khorana diester approach has contributed significantly to the synthesis of a gene sequence.[1] Further the modern triester approach initiated by Letsinger[2] and expanded by Eckstein[3] and Reese[4] has allowed the rapid synthesis of oligodeoxynucleotides in large quantities. Recently Narang has used the triester method to synthesize a 21-unit deoxynucleotide corresponding to the lactose operator of *Escherichia coli.*[5] Unfortunately, because of the presence of the 2′-hydroxyl group, developments in the oligoribonucleotide area have been much slower.

There are three major problems in ribonucleotide synthesis: (1) the selection of suitable protecting groups for the hydroxyl, amino, and phosphate groups; (2) the actual synthesis of nucleosides protected on the 2′-hydroxyl and/or on the 2′- and 5′-hydroxyls; (3) the condensation of the protected nucleosides to nucleotides. Usually several steps are required[6,7] to satisfy requirement 2 and then usually in very low overall yields. The condensation reactions are usually slow and accompanied by low yields, although van Boom[8] has recently reported yields of 40–80% in condensation steps.

Two recent developments have occurred which allow us to present a remarkably simple and rapid synthesis of ribonucleotides. The first development was our application of silyl protecting groups to nucleosides.[9-11] These procedures have now been extended to all of the common ribonucleosides.[12] The only products isolated from the silylation reactions of ribonucleosides are those in which only the hydroxyl groups are protected. Further it is possible to obtain a 2′,5′-disilylated ribonucleoside (**1**) from the parent nucleoside in 40–60% yields in a 30-min reaction.[10,12] Compounds **1** are easily separated

from their 3′,5′-disilylated isomers on silica gel. Thus compounds **1,** protected on the 2′- and 5′-hydroxyls, without protection on exocyclic amino groups, are rapidly obtained.



The second development involves the method of phosphorylative coupling of two nucleosides. Letsinger[13] has recently provided a remarkably fast and mild procedure whereby a dichlorophosphite can be used to couple two nucleosides at −78 °C within 15 min. Rapid iodine oxidation converts the phosphite intermediate to the isolated phosphotriester. Further there is no necessity to protect amino groups[14] using the Letsinger approach.

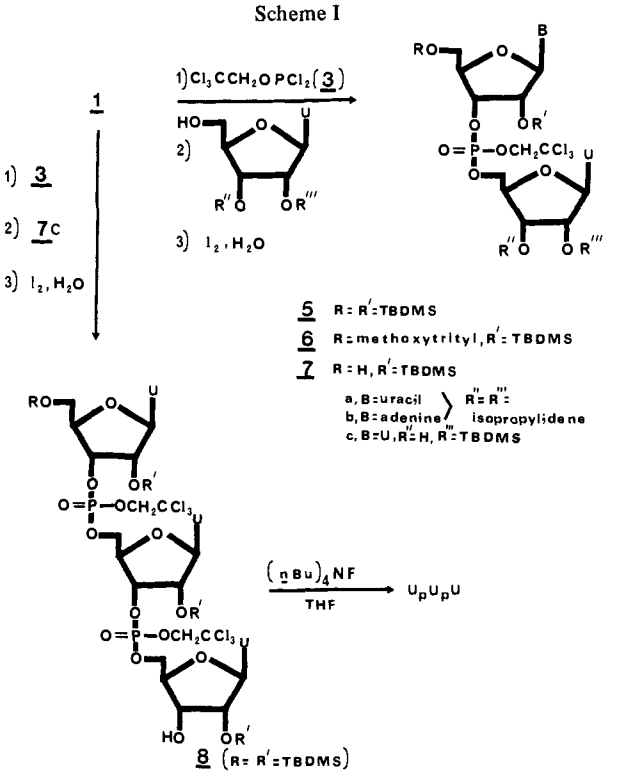
By combining these two developments we have synthesized compounds **5a,b.** To illustrate the procedure,[13] 0.30 g (0.63 mmol) of 2′,5′-disilyluridine in THF (0.5 mL) was added to a solution containing 2,6-lutidine (0.27 mL), 2,2,2-trichloroethyl phosphorodichloridite ($Cl_3CCH_2OPCl_2$, 0.63 mmol), and 0.3 mL of THF at −78 °C. After 30 min, isopropylideneuridine (92 mg, 0.32 mmol) in THF (1.6 mL) was added and after 60 min at −78 °C the solution was allowed to warm to room temperature. The solution was treated with iodine according to the procedure of Letsinger,[13] for 10 min, followed by evaporation of solvents. The residue was dissolved in 10% 1-butanol in chloroform and the solution was extracted with water. After back-extracting the water with chloroform,[13] the combined chloroform extracts were concentrated and applied to silica gel thick layer plates which were developed once in ether. The product separated nicely as a clean band and was eluted from the plate with ethyl acetate. The solvent was evaporated to leave a white solid, **5a** (50%, mp 121–125 °C, R_F^{EtOAc} 0.69). An identical procedure starting with 2′,5′-disilyladenosine (**1b**) gave **5b** (R_F^{EtOAc} 0.56, mp 115–119 °C) in 63% yield.

Both of the compounds **5a** and **5b** were further characterized by removal of the silyl and trichloroethyl protecting groups as described below to yield the respective dinucleotides containing the isopropylidene group. These dinucleotides had properties identical with those of authentic samples on paper chromatography and electrophoresis.

The versatility of this method is illustrated by the synthesis of compounds **5c** and **8** (Scheme I). Since there is a marked difference in the acid lability of a 5′-silyl compared with a 2′-silyl group,[10,12] it is possible to convert compounds **1** into compounds **2** in 60–70% yields. For example, **1a** when heated at 100 °C for 45 min in 80% acetic acid gives a 65% yield of **2a.** The 2′-protecting group in **2** sufficiently screens the 3′-hydroxyl group such that **2** can be condensed with **1** to yield **5c** containing only 3′,5′ linkages. In an experiment 0.63 mmol of **1a** was condensed using the above procedure to produce **5c** (B = uracil) in 60% yield. Compound **5c** was isolated by thick layer chromatography on silica gel using ether–hexane (7:3, two developments) as solvent (R_F^{EtOAc} 0.55, mp 106–112 °C).

While the 5′-silyl group can be selectively removed from **5c** to yield **7c,** under conditions similar to those used to prepare **2,** it is more efficient to use the methoxytrityl groups[16] in **1e.** By starting with **1e,** compound **6c** is obtained in 55% yield (mp 118–121 °C, R_F^{ether} 0.62). Treatment of **6c** with 80% acetic acid at 95 °C for 5 min leads to **7c** (80%, mp 142–146 °C, R_F^{ether} 0.14). Condensation of **7c** with compounds **1** leads to chain extension with the production of **8.** For example the use of **1a** with **7c** leads to a 56% yield of the trinucleotide **8** (R = R′ = TBDMS, mp 145–150 °C, R_F^{ether} 0.40).

Scheme I



The complete simplicity of this method is illustrated by the deblocking of **5c** and **8.** Both the silyl groups and the trichloroethyl groups are removed[15] by dissolving the nucleotide in a solution of tetra-*n*-butylammonium fluoride in THF for 30 min at room temperature. This leads to a quantitative deblocking to produce U_pU and U_pU_pU, respectively which are easily isolated by paper chromatography in standard solvents. The nucleotides so obtained are identical with authentic materials. Thus the deblocking procedure constitutes another major improvement in previously reported syntheses of ribonucleotides.

Thus the procedures described in this report allow for the first time a rapid and efficient synthesis of ribonucleotides. The advantages of the method include (1) rapid synthesis of protected starting materials, (2) use of a single protecting group for hydroxyls, (3) no protection for amino groups, (4) rapid condensation, (5) rapid, quantitative deblocking of the products, and (6) incorporation of all four ribonucleotides into this scheme by the procedures shown.

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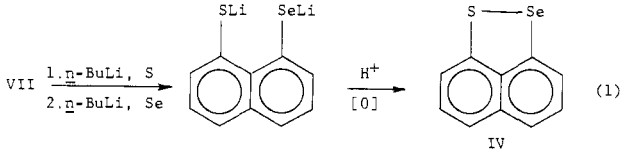
Peri-Bridged Naphthalenes. 2. Unsymmetrical Diatomic Chalcogen Bridges[1]

Sir:

In a previous communication,[2] we reported that 1,8-dilithionaphthalene reacts with elemental sulfur, selenium, and tellurium to yield naphtho[1,8-*cd*]-1,2-dithiole (I), naphtho[1,8-*cd*]-1,2-diselenole (II) and naphtho[1,8-*cd*]-1,2-ditellurole (III), respectively. These compounds are good electron donors and are of particular interest in the formation of "one-dimensional" charge-transfer complexes. We now wish to report the synthesis of the three unsymmetrical members of this series: naphtho[1,8-*cd*]-1,2-selenathiole (IV), naphtho[1,8-*cd*]-1,2-tellurathiole (V), and naphtho[1,8-*cd*]-1,2-telluraselenole (VI). The methodology employed is illustrated by the preparation of the hitherto unknown naphtho[1,8-*cd*]-1,2-selenathiole (IV) in 24% yield from the sequential reaction of 1,8-dibromonaphthalene (VII) with 1



(1)

equiv of *n*-butyllithium, 1 equiv of elemental sulfur, a 2nd equiv of *n*-butyllithium, and 1 equiv of elemental selenium (eq 1). The crude product is isolated as a dark red solid by column chromatography on silica gel using hexane as eluent. Analysis of unpurified IV by GLC and TLC revealed that it contained I and II with the former being the major impurity. When the order of addition of sulfur and selenium is reversed, the results are qualitatively similar: IV is the major product in 29% yield, again accompanied by I and II, although in this case the latter is the major impurity. The formation of these symmetrical by-products probably results from the reaction of the chalcogens with 1,8-dilithionaphthalene. Naphtho[1,8-*cd*]-1,2-selenathiole is a dark red crystalline solid (mp 121–122 °C) whose spectral properties[3] resemble those of the previously synthesized, symmetrical chalcogen-bridged naphthalenes.[2] The characteristic ion intensity ratios of the molecular ion cluster of IV in its 70-eV mass spectrum provide good support for its composition (Table A).

The crystal structure of IV has been determined by x-ray diffraction.[4] Crystals of IV belong to the monoclinic space group $P2_1/c$ with a = 15.417 (6) Å, b = 4.244 (2) Å, c = 16.596 (7) Å, and β = 129.11 (6)°. Density measurements indicated four molecules per unit cell or one per asymmetric unit. All unique data with $2\theta \leq 114°$ were collected on a Syntex $P2_1$ diffractometer using monochromated Cu Kα (1.54178 Å) radiation. A total of 1331 reflections was surveyed, and, after correction for Lorentz, polarization, and background effects, 1076 (81%) were used in the final refinements ($F_o^2 \geq 3\sigma(F_o^2)$). The selenium atom was located using a three-dimensional Patterson synthesis and the nonhydrogen atoms were located on subsequent selenium-phased electron density syntheses. Full-matrix least-squares refinement, with anisotropic temperature factors for the nonhydrogen atoms and omitting hydrogen atoms, has converged to a standard crystallographic residual of 0.078.

Table A. Intensity Ratios of the Molecular Ion Clusters[a-c]

Compound IV			Compound V			Compound VI		
232	2	(2)	280	7	(7)	324	1	(1)
233	0	(0)	281	2	(3)	325	1	(1)
234	19	(18)	282	14	(13)	326	5	(5)
235	18	(17)	283	22	(21)	327	6	(5)
236	49	(49)	284	56	(55)	328	20	(19)
237	7	(8)	285	8	(7)	329	16	(15)
238	100	(100)	286	93	(91)	330	40	(40)
239	12	(12)	287	11	(11)	331	27	(27)
240	22	(23)	288	100	(100)	332	83	(81)
241	3	(3)	289	12	(12)	333	23	(21)
242	1	(1)	290	5	(5)	334	100	(100)
						335	12	(11)
						336	76	(77)
						337	8	(9)
						338	12	(13)
						339	1	(1)

[a] *m/e* intensity observed (calculated). [b] The observed spectra were obtained on an AEI MS-902 instrument. [c] The calculated mass spectra were obtained by use of the MASH computer program, which is a local version of ISOW developed by W. A. G. Graham, University of Alberta, and modified by R. C. Winterton, and R. S. Weber, Cornell University.

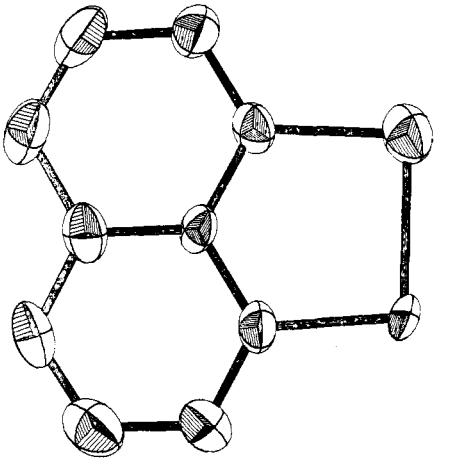
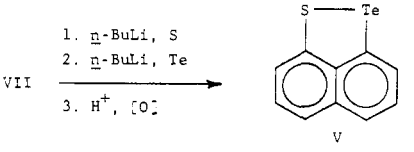


Figure 1. A computer-generated drawing of a single molecule of naphtho[1,8-*cd*]-1,2-selenathiole. Thermal ellipsoids are drawn at the 50% probability level.

Computer generated drawings of the final x-ray model and the extended structure are presented in Figures 1 and 2. The compound is planar and bond angles and distances are in good agreement with accepted values. From the Patterson map and refinement, there is no evidence of disorder with respect to the dichalcogen bridge; indeed the 4.244-Å stacking along the *b* axis (with 25° tilt) is such that the chalcogen atoms form linear chains along the stacking direction.

As summarized in eq 2, VII reacts sequentially with *n*-



(2)