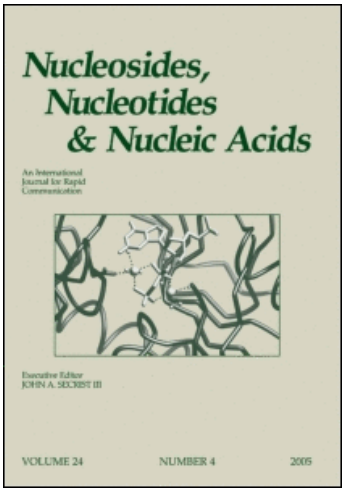

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Electrochemical Removal of Allylic Protecting Groups in Nucleotide Synthesis

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ELECTROCHEMICAL REMOVAL OF ALLYLIC PROTECTING GROUPS IN NUCLEOTIDE SYNTHESIS[a]

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ABSTRACT: Electrochemical, palladium(0)-mediated removal of allylic protecting groups of nucleosides and nucleotides is described. This method required no chromatographic treatment for isolation of the products.

One of the most fundamental problems in nucleic acid synthesis is development of efficient protecting groups that allows mild deprotection and easy separation of the products.[1] Various protecting groups satisfying the former requirement have been invented so far, but they do not always satisfy the latter requirement; the isolation of highly polar nucleic acids is tedious and time-consuming and, in some cases, purification of labile products results in serious decrease of the yield. Allyl[2] for the internucleotide linkage and allyloxycarbonyl (AOC)[3] for the nucleoside base and carbohydrate moieties serve as such efficient protectors, which can be removed by treatment with a Pd(0) catalyst and some nucleophiles. This paper describes a facile method for removal of the allylic protectors from nucleotides based on electrochemical regeneration of a Pd(0) catalyst,[4,5] allowing operationally simple preparation of nucleotides.

Firstly, we investigated electrochemical removal of the *N*- and *O*-allyloxycarbonyl protectors from nucleosides with $Pd[P(C_6H_5)_3]_4$ in a catalytic manner. When N^6-

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[a] This paper is dedicated to the late Dr. Tsujiaki Hata in recognition of his outstanding contribution to nucleic acid science.

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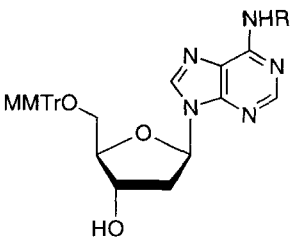
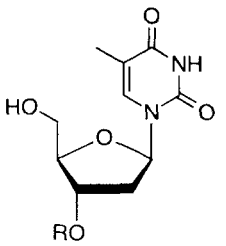
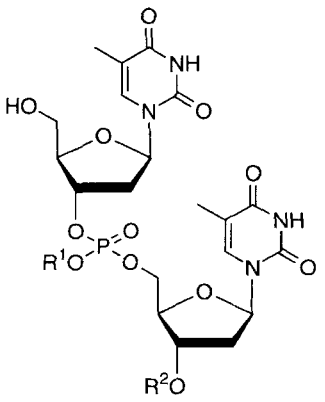
allyloxycarbonylated adenosine **1** was subjected to the electrolysis in the presence of the Pd(0) catalyst using $(n\text{-}C_4H_9)_4NOTs$ as the supporting electrolyte in acetonitrile, the deallyloxycarbonylation proceeded cleanly to provide the N-free adenosine **2** in 88% yield.[6] Similarly, deprotection of the 3'-*O*-allyloxycarbonylated thymidine **3** was achieved using $(n\text{-}C_4H_9)_4NPF_6$ as the supporting electrolyte to give the parent nucleoside **4** in 93% yield.[6] This electrochemical procedure was applicable to remove the allyl protector of phosphoric acid functions including internucleotide linkage. For example, the Pd(0)-catalyzed electrolysis of **5** using $(n\text{-}C_4H_9)_4NPF_6$ as the supporting electrolyte followed by simple extraction furnished an unprotected product. The HPLC (FIGURE 1) showed that the crude material consists of ca. 90% of **6** and a small amount of impurity. The diallylated phosphates, **7**, **9**, **11**, and **13**, also underwent the electrolysis to afford, after deblocking of the 5'-*O*-protector, the corresponding nucleoside 3'-monophosphates, **8**, **10**, **12**, and **14**, respectively.[7] These examples are summarized in TABLE 1.[6]



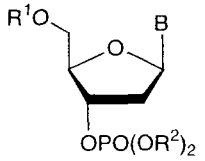
1, R = AOC
2, R = H



3, R = AOC
4, R = H



5, $R^1 = CH_2{=}CHCH_2$; R^2 = AOC
6, $R^1 = R^2 = H$



7, B = Ade; R^1 = MMTr; $R^2 = CH_2{=}CHCH_2$
8, B = Ade; $R^1 = R^2 = H$
9, B = Cyt; R^1 = MMTr; $R^2 = CH_2{=}CHCH_2$
10, B = Cyt; $R^1 = R^2 = H$
11, B = Gua; R^1 = TBDMS; $R^2 = CH_2{=}CHCH_2$
12, B = Gua; $R^1 = R^2 = H$
13, B = Thy; R^1 = MMTr; $R^2 = CH_2{=}CHCH_2$
14, B = Thy; $R^1 = R^2 = H$

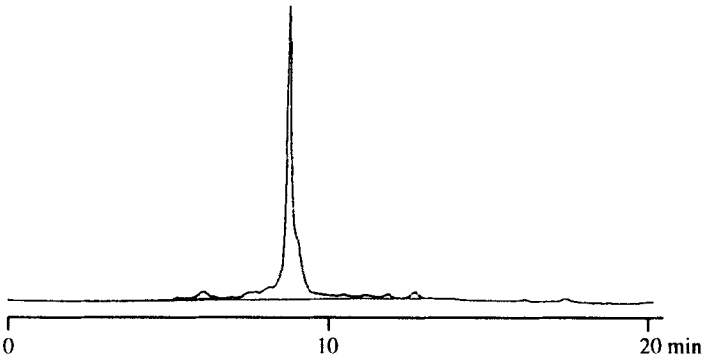


FIGURE 1. HPLC profile of the crude product obtained by electrolysis of **5** [column = nacalai tesque 5C18-AR (4.6-mm diameter, 250-mm length); flow rate = 1 mL/min; temperature = 40 °C].

TABLE 1. Electrochemical Removal of Allylic Protecting Groups with a Palladium(0) Catalyst[a]

compound	F/mole	electrolyte	product	yield, %[b]
1	10	(*n*-C4H9)4NOTs	**2**	88
3	2[c]	(*n*-C4H9)4NPF6	**4**	93
5	2.5	(*n*-C4H9)4NPF6	**6**[d]	90[e]
7	17	(*n*-C4H9)4NOTs	**8**[d,f]	71[g]
9	16	(*n*-C4H9)4NOTs	**10**[d,f]	66[g]
11	17	(*n*-C4H9)4NOTs	**12**[d,h]	76[g]
13	19	(*n*-C4H9)4NOTs	**14**[d,f]	91[g]

[a] Electrolysis was carried out in a single cell (Pt-electrodes), unless otherwise stated. [b] Isolated yield after extractive workup, unless otherwise noted. [c] An H-shape divided cell was used. [d]Triphenylphosphine (0.4 equiv) was added to the reaction mixture. [e] Yield estimated by HPLC. The product is contaminated by ca. 10% of unknown by-products. [f] After electrolysis, the 5'-*O*-*p*-methoxytrityl group was removed by treatment with 80% formic acid. [g] Overall yield after removal of all protecting groups. [h] After electrolysis, the *tert*-butyldimethylsilyl protector of 5'-hydroxyl was deblocked with tetrabutylammonium fluoride.

Choice of the supporting electrolyte, depending on the nature of the products, is important to obtain operational simplicity of the product isolation. In the reaction producing a water-insoluble compound such as **2**, use of water-soluble (n-C_4H_9)$_4$NOTs as the electrolyte is recommended, where the product can be separated very easily from the electrolyte by simple extraction. On the other hand, a hydrophobic electrolyte like (n-C_4H_9)$_4$NPF_6 should be employed in the reaction providing a water-soluble product such as **4** and **6**. In such cases, the water-insoluble electrolyte and the Pd(0) catalyst can be removed at once by extraction in an organic layer. This simplicity is particularly noteworthy.

Thus, we realized a new electrochemical removal of allylic protectors in nucleic acids in conjunction with organo-palladium chemistry. This method is convenient because the nucleic acid product can be isolated without tedious, time-consuming chromatography.

EXPERIMENTAL

General. Melting points (mp) are uncorrected. IR spectra were taken in KBr with a JASCO FT/IR-5300 spectrometer. UV spectra were obtained in methanol on a JASCO V-550 UV–visible light spectrometer. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra in $CDCl_3$ were measured on a JEOL FX-90, JEOL α-400, or JEOL GX-500 instrument. The chemical shifts are described as δ values in ppm relative to Si(CH_3)$_4$ standard for ^{1}H NMR and ^{13}C NMR spectra and to 85% H_3PO_4 standard for ^{31}P NMR spectra. FAB-MS spectra were obtained on a JEOL DX-300 instrument. Elemental analysis was achieved at the Faculty of Agriculture, Nagoya University. HPLC was performed using a Nucleosil column (ODS-7 μm, 300 Å) or Wakosil column (ODS-5 μm, 100 Å) on a JASCO Trirotar-III chromatograph with a JASCO UVIDEC-100-III UV-absorption detector, or COSMOSIL (nacalai tesque, 5C18-AR, 4.6 x 250 mm) on a JASCO 807-IT, PU-980 with a UV-970 detector [solvent A = 5% acetonitrile/triethylammonium acetate buffer; solvent B = 30% acetonitrile/triethylammonium acetate buffer; gradient = 0–2 min (A:B = 10:0), 2–3 min (A:B = 10:0–8:2), 3–33 min (A:B = 8:2–4:6)]. E. Merck Kieselgel 60 (70–230 mesh) deactivated by adding 6% of water or Fuji Silysia BW-300S was used for column chromatography. Electrochemical reactions were carried out with an EG&G MODEL 173 POTENTIOSTAT/GALVANOSTAT.

Solvents and Materials. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl. Acetonitrile was dried over activated molecular sieves 3A and then distilled from CaH_2. All other solvents were employed after simple distillation. Commercially available nucleosides were used after drying by heating at 50–60 °C over P_2O_5 under reduced pressure (1–3 mmHg) or azeotropic removal of water with pyridine. The compounds, **7**, **9**, **11**, and **13** were prepared according to literature methods.[7] *tert*-

Butyllithium in pentane–hexane solution was used after dilution of commercial origin (Aldrich) and determination of the concentration by the Kofron method.[8] Commercially supplied chemical substrates including (n-C4H9)4NOTs (Aldrich), (n-C4H9)4NPF6 (Aldrich or Tokyo Kasei), and Pd[P(C6H5)3]4 (Aldrich) were used without purification.

5'-*O*-(*p*-Methoxytrityl)-N^6-(allyloxycarbonyl)-2'-deoxyadenosine (1) and 5'-*O*-(*p*-Methoxytrityl)-2'-deoxyadenosine (2). A solution of 2'-deoxyadenosine (10.0 g, 40.0 mmol) and *p*-methoxytrityl chloride (12.9 g, 41.6 mmol) in pyridine (120 mL) was stirred at 25 °C for 18 h. To this reaction mixture was poured water (10 mL) and stirring was continued for an additional 1 h. The whole mixture was concentrated to give a gum, which was dissolved in chloroform (300 mL) and washed with brine (200 mL). The aqueous layer was extracted with chloroform (100 mL x 3) and the combined organic solutions were dried. Evaporation followed by column chromatography of the resulting residual oil on silica gel (380 g) using a 1:30 to 1:10 methanol–dichloromethane mixture as eluent produced **2** (14.7 g, 70% yield). An analytical sample, mp 102–103 °C, was obtained by recrystallization from an acetone–benzene mixture. IR 3350, 3200, 1650, 1605, 1580 cm^{-1}; UV λ_{max} 233 nm (ε 20,300); ^1H NMR 2.4–3.0 (m, 2H), 3.40 (d, 2H, J = 5.8 Hz), 3.74 (s, 3H), 4.20 (m, 1H), 4.70 (m, 1H), 6.03 (br s, 2H), 6.43 (t, 1H, J = 6.2 Hz), 6.7–6.9 (m, 2H), 7.2–7.6 (m, 12H), 7.94 (s, 1H), 8.24 (s, 1H). Anal. Calcd for C30H29N5O4: C, 68.82; H, 5.58; N, 13.38. Found: C, 68.61; H, 5.80; N, 13.43.

The product **2** (7.90 g, 15.1 mmol) was dissolved in *N,N*-dimethylformamide (50 mL) and to this solution were added *tert*-butylchlorodimethylsilane (4.16 g, 27.6 mmol) and imidazole (1.17 g, 17.1 mmol). The resulting mixture was stirred at room temperature for 2 h and then poured into water (370 mL). The aqueous solution was extracted with a 1:1 ethyl acetate–hexane mixture (50 mL x 4). The combined organic layers were washed with NaHCO3 solution (25 mL), water (25 mL), and brine (25 mL), and dried. Removal of the organic solvents afforded crystalline product, which was recrystallized from ethyl acetate to give 3'-*O*-(*tert*-butyldimethylsilyl)-5'-*O*-(*p*-methoxytrityl)-2'-deoxyadenosine, mp 181–182 °C (5.20 g, 54% yield from **2**). IR 3320, 3150, 2960, 2930, 2860, 1670, 1610, 1510, 1255, 1110 cm^{-1}; UV λ_{max} 234 (ε 19,700), 260 nm (15,200); ^1H NMR 0.00, 0.06 (two s's, 6H), 0.88 (s, 9H), 2.40 (ddd, 1H, J = 3.9, 6.3, and 13.8 Hz), 2.78 (dq, 1H, J = 13.8 and 6.3 Hz), 3.35 (t, 2H, J = 3.9 Hz), 3.80 (s, 3H), 4.11 (q, 1H, J = 3.9 Hz), 4.5–4.7 (m, 1H), 5.74 (br s, 2H), 6.43 (t, 1H, J = 6.3 Hz), 6.7–6.9 (m, 2H), 7.1–7.8 (m, 12H), 8.03 (s, 1H), 8.33 (s, 1H). Anal. Calcd for C36H43N5O4Si: C, 67.79; H, 6.79; N, 10.98. Found: C, 67.99; H, 6.82; N, 11.09. This product (3.19 g, 5.00 mmol) was dissolved in THF (50 mL) and to the resulting solution was added dropwise at –78 °C a 0.71 M solution of *tert*-butyllithium

in a pentane–hexane mixture (14.0 mL, 10.0 mmol). After stirring for 5 min, allyl 1-benzotriazoyl carbonate (AOC-OBT)[3b] (1.64g, 7.50 mmol) in THF was added over 20 min at the same temperature. The mixture was stirred for 10 min and then the reaction was quenched by adding an aqueous NH_4Cl-saturated solution (4 mL). The whole mixture was evaporated and the resulting residue was treated with brine (80 mL). The aqueous solution was extracted with dichloromethane (30 mL x 3). The combined organic layers were dried and concentrated to give a gummy material (4.10 g), which was subjected to silica gel (75 g) column chromatography and eluted with a 1:1 to 1:1.5 to 1: 2 mixture of ethyl acetate and hexane to afford 3'-*O*-(*tert*-butyldimethylsilyl)-5'-*O*-(*p*-methoxytrityl)-N^6-(allyloxycarbonyl)-2'-deoxyadenosine (3.42 g, 95% yield) as an amorphous solid. IR 2960, 2930, 2860, 1765, 1610, 1580, 1510, 1255, 1105, 1030 cm^{-1}; UV λ_{max} 234 (ε 15,900), 268 nm (19,000); ^1H NMR 0.01, 0.04 (two s's, 6H), 0.86 (s, 9H), 2.41 (ddd, 1H, J = 4.2, 6.0, and 13.2 Hz), 2.79 (fine splitting five lines, 1H, J = 6.0 Hz), 3.34 (dd, 2H, J = 3.0 and 4.2 Hz), 3.78 (s, 3H), 4.0–4.1 (m, 1H), 4.5–4.7 (m, 1H), 4.70 (d, 2H, J = 5.7 Hz), 5.1–5.5 (m, 2H), 5.95 (ddt, 1H, J = 10.2, 17.1, and 5.7 Hz), 6.38 (t, 1H, J = 6.0 Hz), 6.7–6.8 (m, 2H), 7.0–7.4 (m, 12H), 8.08 (s, 1H), 8.63 (s, 1H); ^{13}C NMR –4.8, –4.7, 17.9, 25.7, 40.5, 55.2, 63.6, 66.4, 72.8, 85.1, 86.9, 87.0, 113.3, 122.9, 126.9, 127.7, 128.5, 130.2, 132.0, 135.4, 141.5, 144.1, 149.5, 151.0, 151.2, 152.5, 158.9. To a solution of 3'-*O*-(*tert*-butyldimethylsilyl)-5'-*O*-(*p*-methoxytrityl)-N^6-(allyloxycarbonyl)-2'-deoxyadenosine (138 mg, 0.19 mmol) in THF (3.0 mL) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (0.96 mL, 0.96 mmol). The mixture was stirred at room temperature for 20 min and then concentrated to give an oily material. The crude product was dissolved in ethyl acetate (20 mL) and washed with water (5 mL) followed by brine (5 mL). An oil obtained by evaporation was chromatographed on a silica gel (10 g) column with a 1:15 mixture of methanol and chloroform as eluent to afford the nucleoside **1** as an amorphous solid (113 mg, 97% yield). IR 3400, 2960, 2930, 1755, 1620, 1225 cm^{-1}; UV λ_{max} 233 (ε 15,500), 267 nm (16,000); ^1H NMR 2.42 (d, 1H, J = 4.5 Hz), 2.47 (ddd, 1H, J = 4.5, 6.6, and 13.2 Hz), 2.87 (dq, 1H, J = 13.2 and 6.6 Hz), 3.41 (d, 2H, J = 4.8 Hz), 3.78 (s, 3H), 4.15 (q, 1H, J = 4.2 Hz), 4.6–4.8 (m, 1H), 4.76 (dt, 2H, J = 5.7 and 1.8 Hz), 5.2–5.5 (m, 2H), 6.01 (ddt, 1H, J = 9.6, 16.5, and 5.7 Hz), 6.46 (t, 1H, J = 6.6 Hz), 6.7–6.9 (m, 2H), 7.2–7.5 (m, 12H), 8.10 (s, 1H), 8.47 (s, 1H), 8.68 (s, 1H).

3'-*O*-(Allyloxycarbonyl)thymidine (3). A mixture of thymidine (3.78 g, 15.6 mmol) and a 10% aqueous tetraethylammonium hydroxide solution (18 mL) was stirred at room temperature for 4.5 h. To this mixture was added a solution of AOC-OBT (7.00 g, 31.9 mmol) in THF (150 mL) and stirring was continued for 14 h. The solvent was evaporated to ca. 20 mL of volume and the resulting aqueous layer was extracted with

ethyl acetate (100 mL x 3). The combined organic solutions were dried and concentrated to give a viscous liquid. Column chromatography of this oil on silica gel (110 g) with a 1:30 methanol–chloroform mixture afforded 3',5'-di-*O*-(allyloxycarbonyl)thymidine (813 mg, 13% yield), 3'-*O*-(allyloxycarbonyl)thymidine (**3**) (1.35 g, 27% yield), and 5'-*O*-(allyloxycarbonyl)thymidine (2.01 g, 39% yield) as crystals. An analytical sample of **3**, mp 154–155 °C, was obtained by recrystallization from ethyl acetate. IR 3350, 1760, 1720, 1660, 1300, 1240, 1200 cm^{-1}; UV λ_{max} 265 nm (ε 9,500); ^1H NMR 1.93 (d, 3H, *J* = 1.0 Hz), 2.4–2.6 (m, 2H), 3.93 (dd, 2H, *J* = 2.4 and 11.7 Hz), 4.19 (dd, 1H, *J* = 2.4 and 4.9 Hz), 4.65–4.66 (m, 1H), 5.3–5.4 (m, 3H), 5.94 (ddt, 1H, *J* = 10.2, 17.1, and 5.9 Hz), 6.18 (dd, 1H, *J* = 5.9 and 8.3 Hz), 7.42 (d, 1H, *J* = 1.0 Hz), 8.37 (br s, 1H). Anal. Calcd for $C_{14}H_{18}N_2O_7$: C, 51.52; H, 5.57; N, 8.59. Found: C, 51.71; H, 5.62; N, 8.39.

Allyl 3'-*O*-(Allyloxycarbonyl)thymidylyl(3'-5')-thymidine (5). A mixture of **3** (232 mg, 0.709 mmol), 5'-*O*-(*p,p'*-dimethoxytrityl)thymidine 3'-(allyl *N,N*-diisopropylphosphoramidite[3b] (607 mg, 0.757 mmol), and powdered molecular sieves 3A (10 mg) in acetonitrile (6.0 mL) was stirred at room temperature for 30 min. To this was added 1*H*-tetrazole (212 mg, 3.02 mmol) and stirring was continued for 20 min. A 1.0 M toluene solution of *tert*-butyl hydroperoxide (3.00 mL, 3.00 mmol) was added to the resulting mixture and stirred for 15 min. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with an aqueous sodium hydrogencarbonate solution (10 mL) and brine (10 mL). The organic layer was dried and concentrated. The obtained crude material was subjected to silica gel column chromatography using a 1:9:9 methanol–ethyl acetate–hexane mixture as eluent to afford a glassy oil. This product was dissolved in dichloromethane (22.5 mL) and treated with dichloroacetic acid (1.5 mL) at room temperature for 20 min. The reaction mixture was poured with vigorous stirring into an aqueous solution saturated with sodium hydrogencarbonate (250 mL). The aqueous layer was separated and washed with dichloromethane (15 mL x 2). The combined organic extracts were dried and concentrated to afford a viscous oil, which was chromatographed on silica gel column using a 1:5:5 methanol–ethyl acetate–hexane mixture as eluent to give a diastereomeric mixture of **5** (386 mg, 81% overall yield) as amorphous solid. IR 1701, 1471, 1372, 1263, 1204 cm^{-1}; UV λ_{max} 265 nm (ε 18,600); ^1H NMR 1.90, 1.91 (two s's, 3H), 1.94 (d, 3H, *J* = 0.98 Hz), 2.3–2.4 (m, 1H), 2.46-2.53 (m, 3H), 2.9–3.1 (m, 1H), 3.8–3.9 (m, 2H), 4.2–4.4 (m, 3H), 4.60 (d, 1H, *J* = 7.3 Hz), 4.61 (d, 1H, *J* = 7.3 Hz), 4.65 (d, 2H, *J* = 5.9 Hz), 5.1–5.2 (m, 1H), 5.2–5.3 (m, 1H), 5.32 (dd, 2H, *J* = 0.97 and 10.7 Hz), 5.39 (dd, 2H, *J* = 1.5 and 17.1 Hz), 5.94 (ddt, 2H, *J* = 10.7, 17.1, and 5.9 Hz), 6.14, 6.17 (two dd's, 1H, *J* = 6.3 and 6.3 or 7.3 and 7.3 Hz), 6.30, 6.32

(two dd's, 1H, J = 5.9 and 5.9 Hz), 7.38, 7.39 (two s's, 1H), 7.43 (s, 1H), 8.8–9.1 (m, 2H).; ^{31}P NMR –1.17, –0.92.

Deallyloxycarbonylation of 5'-*O*-(*p*-Methoxytrityl)-N^6-(allyloxycarbonyl)-2'-deoxyadenosine (1): Representative Procedure for Reactions Using (*n*-C4H9)4NOTs as the Supporting Electrolyte. Electrolysis was carried out in a single cell fitted with platinum cathode (2 cm^2) and platinum anode (2 cm^2). A mixture of **1** (60.8 mg, 0.10 mmol), Pd[P(C6H5)3]4 (5.7 mg, 0.005 mmol), and (*n*-C4H9)4NOTs (301 mg, 1.0 mmol) in acetonitrile (10 mL) was charged in the chamber. To this was supplied electricity from the regulated DC power (5.0 mA/cm^2) until the starting material disappeared (10 F/mol, ca. 5.5 h). The resulting mixture was concentrated to give a gum, which was dissolved in dichloromethane (20 mL) and washed with brine. The aqueous layer was extracted with dichloromethane (5 mL x 2). Evaporation of the combined organic layers afforded a solid material. This crude product was dissolved in a small amount of dichloromethane and added to hexane to give precipitates. Filtration gave **2** (46.1 mg, 88% yield, >99% of purity) having the identical ^{1}H NMR spectral data with those of the authentic sample.

Deallylation of **7**, **9**, **11**, and **13** was conducted in a similar manner.

Conversion of Allyl 3'-*O*-(Allyloxycarbonyl)thymidylyl(3'-5')-thymidine (5) to TpT (6): Typical Procedure for Reactions Using (*n*-C4H9)4NPF6 as the Supporting Electrolyte. Electricity (2.5 F/mol) from regulated DC power (5.0 mA/cm^2) was passed through a mixture of **5** (67.1 mg, 0.10 mmol), Pd[P(C6H5)3]4 (5.8 mg, 0.0050 mmol), P(C6H5)3 (0.95 mg, 0.0036 mmol), and (*n*-C4H9)4NPF6 (387 mg, 1.00 mmol) in acetonitrile (20 mL) charged in the chamber. The starting material was consumed after 4 h. The resulting mixture was poured into a 2:3 mixture of water and dichloromethane (50 mL). The organic layer was extracted with water (10 mL x 2). HPLC analysis of the combined aqueous layers indicated that the product contains ca. 90% of TpT (**6**). The evaporation of the aqueous solution gave a gummy oil (72.8 mg) including TpT as a main component.

Removal of the allyloxycarbonyl group from **3** forming **4** was achieved in a similar manner.

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