Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 1699–1702

TETRAHEDRON

An improved large scale synthesis of 1,4-anhydro-4-thio-D-ribitol☆

Noriaki Minakawa,* Yuka Kato, Koichi Uetake, Daisuke Kaga and Akira Matsuda*

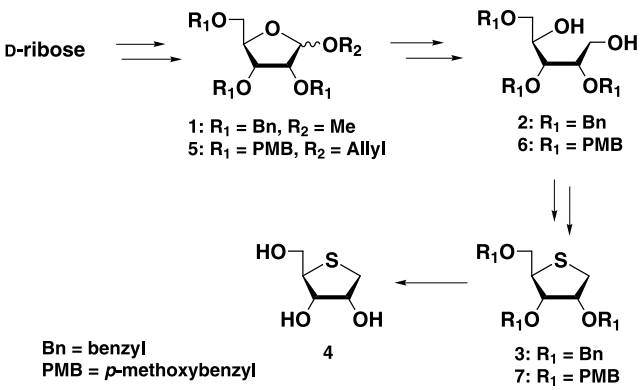
Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan

Received 14 November 2002; accepted 20 January 2003

Abstract—An improved large scale synthesis of 1,4-anhydro-4-thio-D-ribitol (**4**) from D-ribose has been accomplished by combining the *O*-allyl and *O*-*p*-methoxybenzyl protecting groups. Compound **4** was obtained in 31% yield in eight steps with three chromatographic separations. © 2003 Elsevier Science Ltd. All rights reserved.

Over the last decade, there has been increasing interest in the synthesis of 4′-thionucleoside derivatives because of their potent biological activity.[1] Since the 4′-thionucleosides are not available as natural products, condensation of a nucleobase with an appropriate thiosugar is necessary for their synthesis. Although much attention has focused on their biological activity, there are comparatively few literature references for an efficient synthesis of the 4′-thionucleosides.[2] We recently reported the stereoselective synthesis of 4′-thioribonucleosides involving a Pummerer reaction of a sulfoxide derived from 1,4-anhydro-4-thio-D-ribitol (**4**) in the presence of a silylated nucleobase.[3] The reaction afforded the desired β-anomer with the assistance of neighboring group participation. However, in order to develop it as a practical method for the synthesis of the novel 4′-thionucleosides, an efficient synthesis of **4** was required.

As summarized in Scheme 1, compound **4** was prepared by an 11-step synthesis from D-ribose by combining the *O*-methyl and *O*-benzyl protecting groups (**1**→**2**→**3**→**4**). Although, this method has since been shortened to an eight-step synthesis,[4] the last step, namely the debenzylation of **3**, had to be modified in order to apply it to large scale synthesis. Since **3** includes a sulfur atom, the conventional practice of using a palladium catalyst could not be employed. As a result, the reaction was carried out using an excess of BCl_3 at −78°C. In addition, the reaction had to be quenched at the same temperature to furnish **4** in better yield, conditions which made this protocol quite tedious.



Scheme 1.

Consequently, we sought a facile synthesis of **4** that would be applicable to large scale synthesis. To this end, we devised a combination of *O*-allyl and *O*-*p*-methoxybenzyl (*O*-PMB) groups as alternative protecting groups. The *O*-PMB group would be removed under milder conditions than the *O*-benzyl group, while the *O*-methyl protecting group at the 1-position would be replaced by the *O*-allyl group. Using this combination, we developed the improved large scale synthesis of **4** (**5**→**6**→**7**→**4**), also succeeded in minimizing the tedious chromatographic separation of each intermediate. In this paper, details of the synthesis will be described.

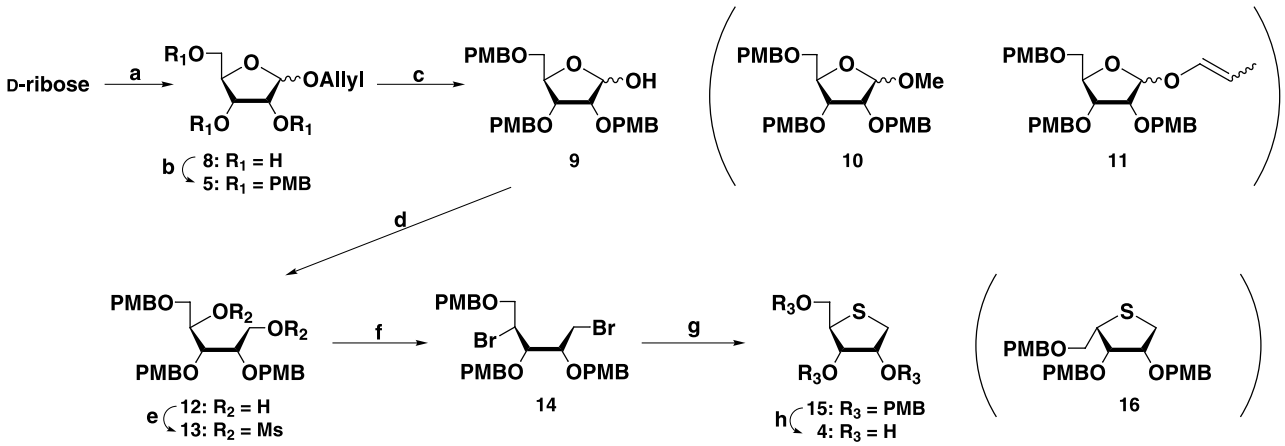
Our synthetic route is illustrated in Scheme 2. The allyl glycosidation of D-ribose was carried out by treatment with allyl alcohol in the presence of a catalytic amount of sulfuric acid.[5] Increasing the amount of allyl alcohol produced a corresponding increase in the yield of **8**, which was ultimately obtained in 95% yield when 70 equiv. of allyl alcohol was used. The remaining hydroxyl groups of **8** were then protected with PMB groups by treatment with PMBCl

☆ This paper constitutes Part 217 of Nucleosides and Nucleotides. Part 216: Sukeda, M.; Ichikawa, S.; Shuto, S.; Matsuda, A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4748–4750.

Keywords: thiosugars; sulfides; protecting groups.

* Corresponding authors. Tel.: +81-11-706-3228; fax: +81-11-706-4980; e-mail: matuda@pharm.hokudai.ac.jp

0040–4020/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00140-6



Scheme 2. *Reagents*: (a) allyl alcohol, H_2SO_4; (b) PMBCl, NaH, THF–DMF; (c) $PdCl_2$, $CHCl_3$–H_2O, O_2, 50°C; (d) $NaBH_4$, MeOH; (e) MsCl, pyridine; (f) LiBr, methyl ethyl ketone, reflux; (g) $Na_2S{\cdot}9H_2O$, DMF, 100°C; (h) 20% TFA in CH_2Cl_2.

Table 1. Deprotection of *O*-allyl ether of **5** with $PdCl_2$

Entry	Solvent	Conditions	Time (h)	Product	Yield (%)
1	MeOH	rt	5	**10**	55
2	$CHCl_3$–H_2O	rt	42	**9**	66
3	$CHCl_3$–H_2O	50°C	27	**9**	73
4	$CHCl_3$–H_2O	50°C/O_2	24	**9**	90

to give **5** in 97% yield. Because of its ease and facility, $PdCl_2$ was selected for the deprotection of the *O*-allyl group to afford **9**. As shown in Table 1, when **5** was treated with $PdCl_2$ in MeOH, the *O*-methyl derivative **10** and not **9** was obtained as the major product in 55% yield (entry 1). Accordingly, the solvent was altered to a mixture of $CHCl_3$–H_2O (1:1), and the desired **9** was obtained in 66% yield; however the reaction rate was slower (entry 2). Although a slight improvement was observed when the reaction mixture was heated at 50°C (entry 3), the starting material **5** was not consumed completely in either case. The results markedly improved when the reaction was carried out under an O_2 atmosphere to give **9** in 90% yield (entry 4).[6] In all cases, the *O*-propenyl intermediate **11** was observed on TLC analysis and was slowly hydrolyzed to give **9**.[6] It should be noted that vigorous stirring of the reaction mixture is essential to complete the reaction.[7] Other conditions such as *t*-BuOK/DMSO,[8] $PdCl_2$/AcONa/AcOH,[9] $NaBH_4/I_2$/THF,[10] or DIBAL/$NiCl_2$(dppp)/toluene[11] did not afford **9** in better yield. Conversion of **9** into **15** was carried out according to our previous method.[4] Thus, **9** was treated with sodium borohydride to give the diol **12** quantitatively. After treatment of **12** with methanesulfonyl chloride in pyridine, the resulting dimesylate **13** was heated under reflux in methyl ethyl ketone in the presence of lithium bromide, followed by treatment with sodium sulfide in DMF to give compound **15**. As in our previous case,[4] the 1,4-anhydro-L-lyxitol derivative **16** was obtained along with **15**. This could be attributed to further substitution of **14** by the bromonium ion, and it was difficult to eliminate this over reaction on a large scale. Although **15** and **16** were obtained as an inseparable mixture, the undesired **16** was an oil, while the desired **15** was obtained as crystals. Therefore, the undesired **16** was removed by crystallization to give the pure **15**. Finally, the PMB groups of **15** were readily removed by treatment with a mixture of TFA–CH_2Cl_2 (1:4) at room temperature to give **4** in 96% yield.

Since the conditions in each step had been optimized, a large scale synthesis of **4** was attempted (see the Experimental Section). In this process, we also tried to avoid the chromatographic separation of each intermediate. Starting with 60 g of D-ribose, compound **12** was prepared in 79% yield in four steps without separation of the intermediates. The resulting **12** was then converted to **15**, which was obtained in 42% yield after crystallization in three steps. Unlike our previous method, the PMB groups of **15** were easily removed to give **4** in 92% yield.

In conclusion, we have developed the facile large scale synthesis of **4**, which was obtained in 31% yield in eight steps from D-ribose even on a large scale. It is worth noting that this synthesis can be carried out using only three chromatographic separations. In addition, use of the PMB group appeared to be advantageous for 4-thiosugar construction. Generally, a benzyl group is used as a protecting group for the synthesis of 4-thiosugars. However, the low reaction temperature and harsh conditions required to deprotect a thiosugar have often proved difficult.[3,12] Since the PMB group can be removed under mild conditions, we think it represents a superior protecting group for the synthesis of 4-thiosugars.

1. Experimental

1.1. General methods

Physical data were measured as follows: Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 270 or 400 MHz and 67.5 or 100 MHz instruments in $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by addition of D_2O. TLC was done on Merck Kieselgel F254 precoated plates. Silica gel used for column chromatography was Merck silica gel 5715.

1.2. Practical synthesis of 1,4-anhydro-4-thio-D-ribitol (4)

1.2.1. 2,3,5-Tri-*O*-*p*-methoxybenzyl-D-ribitol (12). To a solution of D-ribose (60.0 g, 0.4 mol) in allyl alcohol (1.8 L) was added concentrated sulfuric acid (6.4 mL, 0.12 mol) at 0°C, and the mixture was stirred with a mechanical stirrer at room temperature overnight. The reaction mixture was neutralized with sodium bicarbonate. The solids were filtered through a Celite pad, and washed with methanol. The combined filtrate and washings were concentrated in vacuo to give crude **8**.[5] A three-necked flask attached a bubbler was charged with NaH (60% dispersion in mineral oil, 64 g, 1.6 mol) and THF (700 mL). A solution of **8** in DMF (300 mL) was added to the above solution over 3 h at 0°C. After being stirred for 4 h at room temperature, the reaction mixture was cooled to 0°C. About one-third of PMBCl (190 mL, 1.4 mol) was added dropwise to the reaction mixture at the same temperature (10 mL/15 min). Then, the ice-bath was removed, and the remaining PMBCl was carefully added to keep the reaction gentle (Caution! A violent evolution of hydrogen sometimes took place if one added all of the PMBCl at 0°C and then the reaction mixture was warmed to room temperature). After completion of the addition, the reaction mixture was stirred for 24 h at room temperature. The reaction was carefully quenched by addition of saturated aqueous NH_4Cl, and then partitioned between AcOEt and H_2O. The organic layer was further washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo to give the crude **5**. To a solution of **5** in $CHCl_3$–H_2O (1.2 L–800 mL) was added $PdCl_2$ (21.2 g, 0.12 mol), and the two phase solution was vigorously stirred with a mechanical stirrer at 50°C under an O_2 atmosphere. After 24 h, the reaction mixture was filtered through a Celite pad, and washed with AcOEt. The organic solvent was removed in vacuo, and the mixture was diluted with AcOEt. The separated organic layer was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo to give the crude **9**. The resulting **9** was then dissolved in MeOH, and $NaBH_4$ (30.3 g, 0.8 mol) was added portionwise at 0°C. After being stirred for 1.5 h at room temperature, the solvent was removed in vacuo. The residue was partitioned between AcOEt and H_2O. The separated organic layer was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (5:1–1:1), to give **12** (162.4 g, 79% as a colorless oil): FAB-LRMS *m/z* 513 (MH^+, 1.9%); FAB-HRMS calcd for $C_{29}H_{37}O_8$ (MH^+) 513.2489, found 513.2486; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25–7.15 (m, 6H), 6.88–6.82 (m, 6H), 4.66–4.40 (m, 6H), 3.95 (m, 1H), 3.78 (m, 11H), 3.72 (m, 2H), 3.54 (m, 2H), 2.67 (br s, 1H), 2.37 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.15, 129.96, 129.92, 129.81, 129.64, 129.44, 113.77, 113.72, 113.69, 78.89, 78.82, 73.56, 73.01, 71.51, 70.66, 70.59, 60.99, 55.23.

1.2.2. Physical data for allyl 2,3,5-tri-*O*-*p*-methoxybenzyl-D-ribofuranose (5). FAB-LRMS *m/z* 573 (MNa^+, 51.9%); FAB-HRMS calcd for $C_{32}H_{38}NaO_8$ (MNa^+) 573.2464, found 573.2490; ^{1}H NMR of isomer A (400 MHz, $CDCl_3$) δ: 7.30–7.18 (m, 6H), 6.87–6.81 (m, 6H), 5.81 (dddd, 1H, *J*=17.3, 10.3, 6.2, 5.5 Hz), 5.20 (dd, 1H, *J*=17.3, 1.2 Hz), 5.13 (dd, 1H, *J*=10.3, 1.2 Hz), 5.02 (s, 1H), 4.61–4.31 (m, 6H), 4.29 (ddd, 1H, *J*=6.7, 6.2, 3.8 Hz), 4.15 (dd, 1H, *J*=12.9, 5.5 Hz), 3.98 (dd, 1H, *J*=6.7, 4.7 Hz), 3.90 (dd, 1H, *J*=12.9, 6.2 Hz), 3.85 (d, 1H, *J*=4.7 Hz), 3.80, 3.79, 3.78 (each s, each 3H), 3.56 (dd, 1H, *J*=10.6, 3.8 Hz), 3.46 (dd, 1H, *J*=10.6, 6.2 Hz); ^{13}C NMR of isomer A (100 MHz, $CDCl_3$) δ: 159.16, 159.08, 158.93, 134.03, 130.30, 129.83, 129.50, 129.35, 129.12, 128.52, 117.13, 113.83, 113.67, 113.60, 113.57, 104.41, 104.38, 80.46, 79.26, 78.09, 72.70, 71.93, 71.88, 71.10, 68.18, 55.24; ^{1}H NMR of isomer B (400 MHz, $CDCl_3$) δ: 7.26–7.12 (m, 6H), 6.85–6.79 (m, 6H), 5.98 (dddd, 1H, *J*=17.3, 10.3, 6.5, 5.9 Hz), 5.32 (dd, 1H, *J*=17.3, 1.3 Hz), 5.18 (dd, 1H, *J*=10.3, 1.3 Hz), 5.02 (d, 1H, *J*=4.1 Hz), 4.71–4.33 (m, 6H), 4.27 (m, 1H, *J*=13.2, 4.1 Hz), 4.21 (m, 1H), 4.13 (dd, 1H, *J*=13.2, 6.7 Hz), 3.81, 3.80, 3.79 (each s, each 3H), 3.74 (m, 2H), 3.38 (dd, 1H, *J*=10.6, 3.8 Hz), 3.31 (dd, 1H, *J*=10.6, 4.4 Hz); ^{13}C NMR of isomer B (100 MHz, $CDCl_3$) δ: 159.09, 159.01, 158.97, 134.60, 130.25, 129.91, 129.86, 129.67, 129.48, 129.13, 117.21, 113.60, 113.58, 113.48, 99.95, 81.82, 77.09, 74.59, 72.98, 71.87, 71.69, 69.68, 68.52, 55.22.

1.2.3. Physical data for 2,3,5-tri-*O*-*p*-methoxybenzyl-D-ribofuranose (9). FAB-LRMS *m/z* 509 ($M-H^+$, 1.4%); FAB-HRMS calcd for $C_{29}H_{33}O_8$ ($M-H^+$) 509.2176, found 509.2163; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30–7.16 (m, 6H), 6.87–6.82 (m, 6H), 5.28–5.23 (m, 1H), 4.63–4.08 (m, 8H), 3.80–3.78 (m, 9H), 3.60 (m, 0.5H), 3.41 (m, 2.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.24, 159.19, 159.06, 128.84, 129.74, 129.70, 129.58, 129.51, 129.43, 129.31, 129.24, 129.10, 113.75, 113.72, 113.68, 113.66, 100.29, 100.25, 96.19, 96.16, 80.89, 80.29, 77.26, 77.14, 73.08, 72.29, 72.00, 71.98, 71.96, 71.84, 69.65, 68.99, 55.24.

1.2.4. 1,4-Anhydro-2,3,5-tri-*O*-*p*-methoxybenzyl-4-thio-D-ribitol (15). To a solution of **12** (162 g, 0.32 mol) in dry pyridine (900 mL) was added methanesulfonyl chloride (122 mL, 1.6 mol) at 0°C. After being stirred for 30 min at the same temperature, the reaction was quenched by addition of ice. The reaction mixture was partitioned between AcOEt and H_2O. The separated organic layer was washed with saturated aqueous $NaHCO_3$ (three times), followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was coevaporated several times with toluene to give the dimesylate **13**. The crude **13** was dissolved in methyl ethyl ketone (1 L), and well-dried lithium bromide (278 g, 3.2 mol) was added to the solution. The mixture was heated under reflux for 12 h. After being cooled to room temperature, the mixture was diluted with AcOEt and washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give the crude **14**. The resulting **14** was dissolved in DMF (1 L), and sodium sulfide nonahydrate (92.2 g, 0.38 mol) was added to the solution. The mixture was heated at 100°C for 30 min. After being cooled to room temperature, the mixture was diluted with AcOEt and washed with H_2O (three times), followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (10:1–1:1), to give **15** including **16** (121.5 g, 63%, **15**/**16**=7:1). The resulting product was crystallized from hexane–AcOEt to give pure **15** as white

crystals (69.1 g, 42%): mp 82°C; FAB-LRMS *m/z* 511 (MH^+, 1.8%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25–7.19 (m, 6H), 6.87–6.81 (m, 6H), 4.55–4.39 (m, 6H), 3.97 (ddd, 1H, *J*=7.0, 5.6, 3.8 Hz), 3.90 (dd, 1H, *J*=3.8, 4.1 Hz), 3.81 (s, 9H), 3.63 (m, 1H), 3.43 (m, 2H), 2.99 (dd, 1H, *J*=7.0, 10.6 Hz), 2.84 (dd, 1H, *J*=5.6, 10.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.11, 130.14, 130.09, 129.48, 129.19, 113.72, 113.64, 80.45, 79.24, 72.69, 71.67, 71.45, 71.35, 55.29, 47.23, 30.79. Anal. calcd for $C_{29}H_{34}O_6S$: C, 68.21; H, 6.71. Found: C, 68.17; H, 6.87.

1.2.5. Physical data for 1,4-Anhydro-2,3,5-tri-*O*-*p*-methoxybenzyl-4-thio-L-lyxitol (16). FAB-LRMS *m/z* 509 ($M-H^+$, 4.0%); FAB-HRMS calcd for $C_{29}H_{33}O_6S$ ($M-H^+$) 509.1998, found 509.2004; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25–7.21 (m, 6H), 6.87–6.82 (m, 6H), 4.76 (d, 1H, *J*=11.4 Hz), 4.59 (d, 1H, *J*=11.4 Hz), 4.49 (s, 2H), 4.42 (m, 2H), 4.13 (dd, 1H, *J*=3.2, 3.8 Hz), 3.99 (ddd, 1H, *J*=3.2, 6.2, 9.4 Hz), 3.80 (m, 10H), 3.50 (m, 2H), 3.02 (dd, 1H, *J*=9.4, 9.7 Hz), 2.87 (dd, 1H, *J*=6.2, 9.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.14, 159.10, 159.02, 130.75, 130.21, 130.10, 129.34, 128.96, 113.78, 113.73, 113.58, 83.22, 78.26, 73.15, 72.96, 71.82, 69.90, 55.29, 45.80, 30.43.

1.2.6. 1,4-Anhydro-4-thio-D-ribitol (4).[3] To a solution of **15** (69 g, 135 mmol) in dry CH_2Cl_2 (560 mL) was added trifluoroacetic acid (140 mL) at room temperature, and the mixture was stirred for 2 h at the same temperature. The solvent was removed in vacuo, and the residue was coevaporated with MeOH several times. The resulting precipitates were filtered off, washed with MeOH. The solvent was removed in vacuo, and the residue was purified by a silica gel column, eluted with MeOH in $CHCl_3$ (2–10%), to give **4** (18.7 g, 92% as a yellow oil).

Acknowledgements

This invastigation was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science, Sports, and Culture of Japan. We would like to thank Ms H. Matsumoto and Ms A. Maeda (Center for Instrumental Analysis, Hokkaido University) for elemental analysis. We also would like to thank Ms S. Oka (Center for Instrumental Analysis, Hokkaido University) for measurement of Mass spectra.

References

1. For examples, see; (a) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Med. Chem.* **1991**, *34*, 2782–2786. (b) Secrist, J. A., III.; Tiwari, K. N.; Riordan, J. M.; Montgomery, J. A. *J. Med. Chem.* **1991**, *34*, 2361–2366. (c) Van Draanen, N. A.; Freeman, G. A.; Short, S. A.; Harvey, R.; Jansen, R.; Szczech, G.; Koszalka, G. W. *J. Med. Chem.* **1996**, *39*, 538–542. (d) Rahim, S. G.; Trivedi, N.; Bogunovic-Batchelor, M. V.; Hardy, G. W.; Mills, G.; Selway, J. W. T.; Snowden, W.; Littler, E.; Coe, P. L.; Basnak, I.; Whale, R. F.; Walker, R. T. *J. Med. Chem.* **1996**, *39*, 789–795. (e) Yoshimura, Y.; Kitano, K.; Yamada, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 3140–3152. (f) Yoshimura, Y.; Watanabe, M.; Satoh, H.; Ashida, N.; Ijichi, K.; Sakata, S.; Machida, H.; Matsuda, A. *J. Med. Chem.* **1997**, *40*, 2177–2183. (g) Secrist, J. A., III.; Tiwari, K. N.; Shortnacy-Fowler, A. T.; Messini, L.; Riordan, J. M.; Montgomery, J. A.; Meyers, S. C.; Ealick, S. E. *J. Med. Chem.* **1998**, *41*, 3865–3871.
2. (a) Haraguchi, K.; Nishikawa, A.; Sasakura, E.; Tanaka, H.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron Lett.* **1998**, *39*, 3713–3716. (b) Inguaggiato, G.; Jasamai, M.; Smith, J. E.; Slater, M.; Simons, C. *Nucleosides Nucleotides* **1999**, *18*, 457–467. (c) Wang, Y.; Inguaggiato, G.; Jasamai, M.; Shah, M.; Hughes, D.; Slater, M.; Simons, C. *Bioorg. Med. Chem.* **1999**, *7*, 481–487. (d) Naka, T.; Nishizono, N.; Minakawa, N.; Matsuda, A. *Tetrahedron Lett.* **1999**, *40*, 6297–6300.
3. Naka, T.; Minakawa, N.; Abe, H.; Kaga, D.; Matsuda, A. *J. Am. Chem. Soc.* **2000**, *122*, 7233–7243.
4. Minakawa, N.; Kaga, D.; Kato, Y.; Endo, K.; Tanaka, M.; Sasaki, T.; Matsuda, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2182–2189.
5. Finch, P.; Iskander, G. M.; Siriwardena, A. H. *Carbohydr. Res.* **1991**, *210*, 319–325.
6. (a) Mereyala, H. B.; Guntha, S. *Tetrahedron Lett.* **1993**, *34*, 6929–6930. (b) Mereyala, H. B.; Lingannagura, S. R. *Tetrahedron* **1997**, *53*, 17501–17512.
7. If the *O*-propenyl derivative **11** was not consumed, the reaction mixture was successively treated with 10% trifluoroacetic acid in aqueous THF (TFA/THF/H_2O=1:4:5) to give **9** completely.
8. Cunningham, J.; Gigg, R.; Warren, C. D. *Tetrahedron Lett.* **1964**, 1191–1196.
9. Smith, III., A. B.; Rivero, R. A.; Hale, K. J.; Vaccaro, H. V. *J. Am. Chem. Soc.* **1991**, *113*, 2092–2112.
10. Thomas, R. M.; Mohan, G. H.; Iyengar, D. S. *Tetrahedron Lett.* **1997**, *38*, 4721–4724.
11. Taniguchi, T.; Ogasawara, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1136–1137.
12. For examples: (a) Hancox, E. L.; Walker, R. T. *Nucleosides Nucleotides* **1996**, *15*, 135–148. (b) De Valette, F.; Barascut, J.-L.; Imbach, J.-L. *Nucleosides Nucleotides* **1998**, *17*, 2289–2310. (c) Otter, G. P.; Elzagheid, M. I.; Jones, G. D.; MacCulloch, A. C.; Walker, R. T.; Oivanen, M.; Klika, K. D. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2343–2349. (d) Wirsching, J.; Voss, J. *Eur. J. Org. Chem.* **1999**, 691–696. (e) Wirsching, J.; Voss, J.; Adiwidjaja, G.; Balzarini, J.; De Clercq, E. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 1625–1645.