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The First Radical Method for the Introduction of an Ethynyl Group Using a Silicon Tether and Its Application to the Synthesis of 2′-Deoxy-2′-*C*-ethynylnucleosides[1]

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Received October 22, 2002

A novel radical method for the stereoselective introduction of an ethynyl group has been developed. When a solution of ethynyldimethylsilyl (EDMS) or [2-(trimethylsilyl)ethynyl]dimethylsilyl (TEDMS) ethers of *trans*-2-iodoindanol was treated with Et_3B followed by tetrabutylammonium fluoride in toluene, atom transfer 5-*exo*-cyclization and subsequent elimination occurred to give *cis*-2-ethynylindanol in high yield. The method was shown to be useful in the introduction of an ethynyl group in various five- and six-membered-ring iodohydrins. Furthermore, 2′-deoxy-2′-*C*-ethynyluridine (**6**) and -cytidine (**7**), which were designed as novel antimetabolites, were readily synthesized by using this method as the key step. This would be the first example in which a radical reaction was used for introducing an ethynyl group.

Introduction

Ethynyl groups, which have characteristic electronic and structural features due to sp hybridization, are present in many biologically active compounds.[2] For examples, an anti-Parkinsonian selegiline,[3a] a synthetic follicle hormone ethynylestradiol,[3b] and an anti-human immunodeficiency virus (HIV) agent efavirenz,[3c] the structures of which are shown in Figure 1, have proven effective in clinical use. Accordingly, in the course of structure−activity relationship studies for drug development, the introduction of ethynyl groups into compounds is often attempted. Effective methods for regio- and/or stereoselective introduction of ethynyl groups should therefore be very useful.[4]

We have been engaged in medicinal chemical studies of nucleoside analogues[5] and have found that the introduction of an ethynyl group into the natural nucleoside structure sometimes produces potent anti-metabolites. 5-Ethynyl-4-carbamoylimidazole-1-*β*-D-riboside (EICAR, **1**) has shown anti-RNA viral and antitumor effects due to its inosine 5′-phosphate dehydrogenase inhibition.[6] 1-(3-*C*-Ethynyl-*β*-D-*ribo*-pentofuranosyl)cytosine (ECyd, **2**) is a potent antitumor nucleoside that significantly inhibits the growth of various human solid tumor cells both in vitro and in vivo, probably due to the inhibition of tumor RNA synthesis.[7] 2′-Deoxy-4′-*C*-ethynylthymidine (**3**) was identified as a potent anti-HIV agent,[8] which is effective against multidrug-resistant HIV strains isolated from patients.[8c,d] Furthermore, the adenosine derivatives **4**[9] and **5**[10] having ethynyl groups were identified as potent purinoceptor ligands.

These encouraging results prompted us to synthesize further ethynyl nucleosides, such as 2′-deoxy-2′-*C*-ethynyluridine (**6**) and 2′-deoxy-2′-*C*-ethynylcytidine (**7**). How-

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(1) This publication constitutes Part 219 of the series Nucleosides and Nucleotides: for Part 218 see: Ueno, Y.; Hoshika, S.; Shibata, A.; Jin, J.; Kitade, Y.; Matsuda, A. *Bioorg. Med. Chem*. Submitted for publication.

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10.1021/jo0206667 CCC: $25.00
Published on Web 04/09/2003

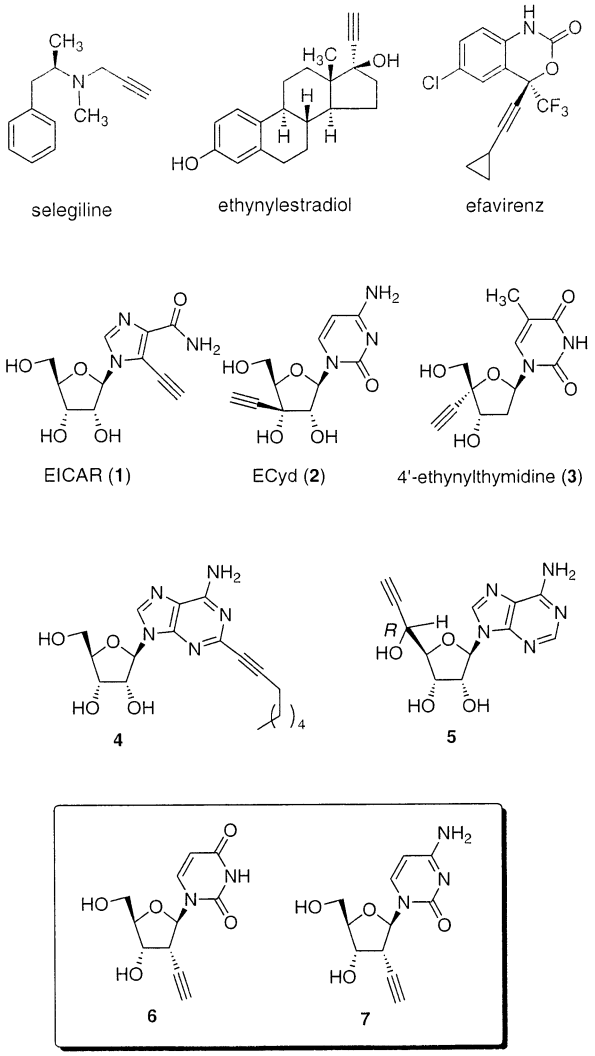

FIGURE 1. Biologically active compounds having an ethynyl group and the target ethynylnucleosides **6** and **7**.

ever, the regioselective introduction of an ethynyl group into nucleosides, especially into the sugar moiety in a stereoselective manner, is problematic, and the previous syntheses of the ethynyl nucleosides **2** and **3** required rather long reaction pathways.[7,8]

Ethynyl groups are also very useful in synthetic organic chemical studies, and accordingly, much effort has been expended to develop efficient methods for introducing ethynyl and/or substituted ethynyl groups into compounds, which produce alkynes via C−C single bond formation.[4] These methods can be generally classified as Type A, reactions of an acetylide or its congeners to electrophilic carbon centers, and Type B, reactions of an alkyne having an attached leaving group to nucleophilic carbon centers, as shown in Scheme 1 paths a and b.[11] Type A includes reactions of alkynylmetals with carbon electrophiles[12] and transition metal-catalyzed cross-coupling reactions with alkyne derivatives.[13] Type B is typified by reactions between an alkynyl halide and a carbon nucleophile, which appear to proceed via an addition−elimination mechanism.[14] Although these reactions are very effective, introduction of an ethynyl group at aliphatic carbon centers is often troublesome, especially regio- and stereoselectively. In fact, the synthesis of our target ethynyl nucleosides **6** and **7**, having a *cis*-ethynylalkanol structure, was likely to be rather difficult.

We thought that radical reactions[15] with silicon-containing tethers, which have been widely used for forming C−C bonds,[16] might be employed effectively for introducing ethynyl groups, as shown in Scheme 1c.Recently, we developed a regio- and stereoselective method for introducing C2-units at the position β to a hydroxyl

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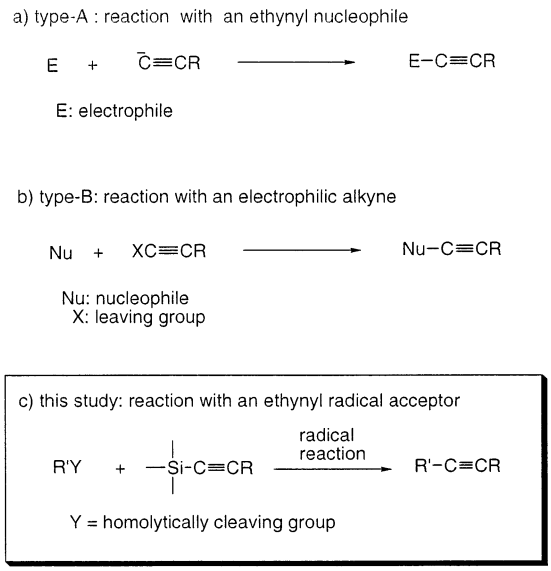
SCHEME 1



group in halohydrins or α-phenylselenoalkanols using a radical cyclization reaction with a dimethyl- or diphenylvinylsilyl group as a temporary connecting radical-acceptor tether (Scheme 2).[17] Thus, the selective introduction of both the 1-hydroxyethyl and the 2-hydroxyethyl groups can be achieved, depending on the concentration of Bu_3SnH in the reaction system, via a 5-*exo*-cyclization intermediate **E** or a 6-*endo*-cyclization intermediate **F**, respectively, after ring-cleavage of the radical reaction products by their oxidative treatment, as shown in Scheme 2.[17a,b] The studies on the mechanism showed that the kinetically favored 5-*exo*-cyclized radical **C**, formed from radical **B**, was trapped when the concentration of Bu_3SnH was high enough to give **E**. At lower concentrations of Bu_3SnH and higher reaction temperatures, radical **C** rearranged into the more stable ring-enlarged 4-oxa-3-silacyclohexyl radical **D**, which was then trapped with Bu_3SnH to give **F**. This ring-enlarging rearrangement was proved to occur via a pentavalent-like silicon-bridging transition state **X**.[17g] A vinyl group can also be introduced when the radical reaction is carried out under the atom-transfer conditions, i.e., in the absence of a hydrogen source such as Bu_3SnH: a photoreaction of the vinylsilyl ether **A** in the presence of $(Bu_3Sn)_2$, followed by treatment of the resulting atom-transfer 5-*exo*-cyclization product **I** with fluoride ion forms the vinyl product **J**.[17d] These reactions have been successfully applied to the synthesis of biologically important 4′-branched-chain sugar nucleosides[17b,c] and *C*-glycosides.[17e,h]

We hoped to develop a new radical method for introducing an ethynyl group based on these previous results with a temporary silicon connection. Such a radical method, as shown in Scheme 1c, would be a new type of method for the introduction of ethynyl groups, which is clearly different from the previous ionic type A and type B reactions.

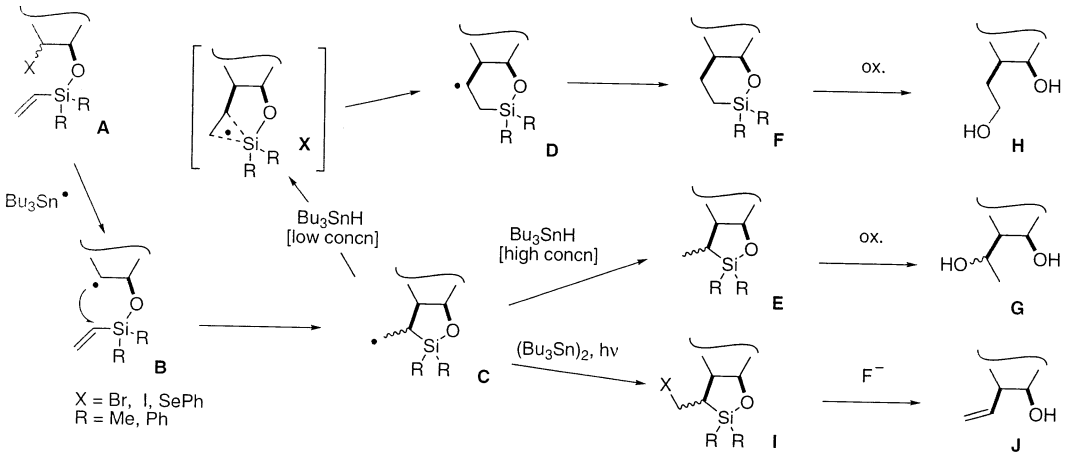
In this report, we describe a new efficient method for the regio- and stereoselective introduction of an ethynyl group by adapting an atom-transfer radical cyclization reaction[18,19] with an ethynylsilyl group as the radical acceptor tether.[20] Application of the new method to the synthesis of 2′-deoxy-2′-*C*-ethynyluridine (**6**) and 2′-deoxy-2′-*C*-ethynylcytidine (**7**) is also described.

Results and Discussion

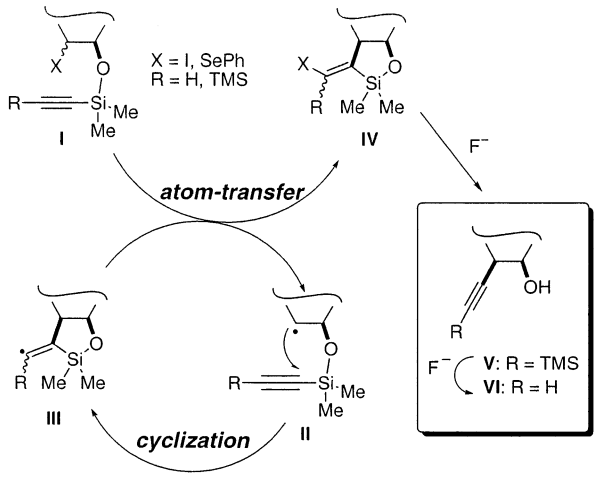
Working Hypothesis. Our strategy, using ethynyldimethylsilyl (EDMS) or [2-(trimethylsilyl)ethynyl]dimethylsilyl (TEDMS)[21] ethers of iodohydrins or α-phenylselenoalkanols (**I**) as the reaction substrates, is shown in Scheme 3. Treatment of the substrate **I** with a radical initiator would produce the radical **II**, which preferentially 5-*exo*-cyclizes to produce the radical **III**. When the radical reaction is performed under atom-transfer conditions,[22] i.e., in the absence of a hydrogen source, the radical **III** would abstract the iodine atom[23] or PhSe group[24] of another substrate **I** to reproduce the radical **II** along with the atom-transfer cyclization product **IV**. Turnover of this scheme would accumulate the desired product **IV**. We anticipated that, if this indeed occurred, subsequent treatment of the product **IV** with fluoride ion would promote elimination[25] to give the desired ethynyl product **V**. Thus, using the reaction sequence, the regio- and stereoselective introduction of an ethynyl group at the position *β*-cis to a hydroxyl group in iodohydrins or α-phenylselenoalkanols would be achieved.[26]

Reaction with Model Indanol Substrates. We first planned to investigate the reaction with TEDMS ethers of the indanols, **10a** and **11a**, as model substrates. The TEDMS tether was introduced into the hydroxyl of *trans*-

SCHEME 2

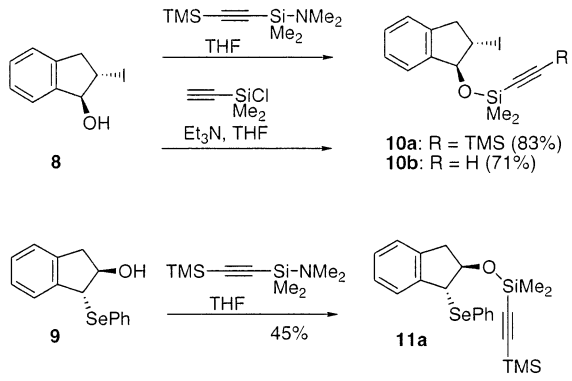


SCHEME 3



2-iodoindanol (**8**) and *trans*-1-phenylseleno-2-indanol (**9**) with TEDMS−NMe_2[27] as shown in Scheme 4. Since the expected atom-transfer radical cyclization product, i.e., **IV** in Scheme 3, was thought to be unstable, tetrabutylammonium fluoride (TBAF, 2.5 equiv) was added directly to the reaction mixture after the starting material had disappeared on TLC. The resulting product of the reaction sequence was isolated as the corresponding 3,5-dinitrobenzoate by treatment with 3,5-dinitrobenzoyl (DNBz) chloride, Et_3N, and DMAP in MeCN. The results are summarized in Table 1.

SCHEME 4



The iodoindanol substrate **10a** was heated in the presence of $(Bu_3Sn)_2$ (1.0 equiv) and AIBN (0.6 equiv) in benzene to give the expected *cis*-2-ethynylindanol **12** and its dinitrobenzoate **12′** [28] in 40% yield (entry 1). When the radical reaction was carried out by irradiating a solution of **10a** in benzene containing $(Bu_3Sn)_2$ (0.1 equiv) with a high-pressure mercury lamp at room temperature, the yield of **12′** increased to 71% (entry 2). Excellent results were observed when Et_3B (0.3 equiv) was used as a radical initiator to produce the desired product **12′** in 84% yield (entry 3).[29] On the other hand, none of the ethynyl product **13′** was obtained in the reactions with the 1-phenylselenoindanol substrate **11a** (entries 5−7). In these experiments, TLC analysis suggested that the radical cyclization did not occur.

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(19) Atom-transfer radical cyclization reactions, for examples see: (a) Chow, Y. L.; Perry, R. A. *Can. J. Chem.* **1985**, *63*, 2203−2210. (b) Bernardi, A.; Cardani, S.; Poil, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 5043−5045. (c) Curran, D. P.; Chang, C. T. *Tetrahedron Lett.* **1987**, *28*, 2477−2480. (d) Haaima, G.; Weavers, T. *Tetrahedron Lett.* **1988**, *29*, 1085−1088. (e) Lee, G. M.; Parvez, M.; Weinreb, S. M. *Tetrahedron* **1988**, *44*, 4671−4678. (f) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826−1831. (g) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738−6740. (h) Byers, J. H.; Gleason, T. G.; Knight, K. S. *J. Chem. Soc., Chem. Commun.* **1991**, 354−356. (i) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746−2750. (j) Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B.; Vassalo, M. *Tetrahedron* **1992**, *48*, 3945−3960. (k) Curran, D. P.; Geib, S. J.; Lin, C. H. *Tetrahedron: Assmetry* **1994**, *5*, 199−202. (l) Martinez-Grau, A.; Curran, D. P. *J. Org. Chem.* **1996**, *60*, 8332−8333. (m) Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94−103.

(20) A preliminary account of this study: Sukeda, M.; Ichikawa, S.; Matsuda, A.; Shuto, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 4748−4750.

(21) Radical cyclization reactions with a TEDMS group as a tether have been reported: (a) Xi, Z.; Rong, J.; Chattopadhyaya, J. *Tetrahedron* **1994**, *50*, 5255−5272. (b) Skrydstrup, T.; Mazéas, D.; Elmouchir, M.; Doisneau, G.; Riche, C.; Chiaroni, A.; Beau, J.-M. *Chem. Eur. J.* **1997**, *3*, 1342−1356.

(22) Atom-transfer radical cyclization reactions to a C≡C bond: (a) Curran, D. P.; Chen, M. H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489−2490. (b) Ichinose, Y.; Matsunaga, S.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 3155−3158.

(23) Atom transfer radical reactions effectively occur via a homolytic C−I bond cleavage, see: (a) Curran, D. P.; Kim, D. *Tetrahedron Lett.* **1986**, *27*, 5821−5824. (b) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477−2480. (c) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746−2750. (d) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604−8605.

(24) Radical atom transfer reactions occur via a homolytic C−Se bond cleavage when a phenylseleno group is attached at a benzylic position: ref 17d

(25) Fluoride ion promoted elimination of 2-halogenovinylsilines to produce alkynes has been reported: (a) Yamaguchi, R.; Kawasaki, H.; Yoshitome T.; Kawanishi H. *Chem. Lett.* **1982**, 1485−1486. (b) Shakespeare, W. C.; Johnson, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 8578−8579. (c) Schmitz, C.; Rouanet-Dreyfuss, A.-C.; Tueni, M.; Biellmann, J.-F. *J. Org. Chem.* **1996**, *61*, 1817−1821. (d) Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630−633.

(26) Formyl group-transfer or cyano group-transfer radical reactions have been reported: (a) Cossy, J.; Poitevin, C.; Pardo, D. G.; Peglion, J. L. *Synthesis* **1995**, 1368−1370. (b) Jung, M. E.; Tina, C. S. W. *Tetrahedron Lett.* **1993**, *34*, 6247−6250.

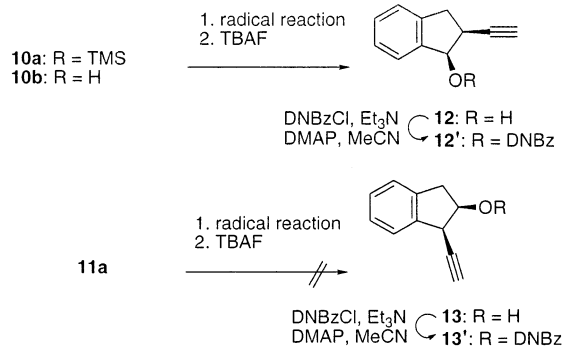
(27) Stork, G.; Keitz, P. F. *Tetrahedron Lett.* **1989**, *30*, 6981−6984.

TABLE 1. Atom-Transfer Radical Cyclization and Subsequent Elimination Reaction of Indanol Substrates, 10a, 11a, and 10b[a]

		radical reaction conditions		
entry	substrate	reagents[b]/temp/solvent	product	yield, %
1	**10a**	A/80 °C/benzene	**12′**	40
2	**10a**	B/rt/benzene	**12′**	71
3	**10a**	C/rt/toluene	**12′**	84
4	**10a**	D/rt/toluene	**12′**	7
5	**11a**	A/80 °C/benzene	**13′**	0
6	**11a**	B/rt/benzene	**13′**	0
7	**11a**	C/rt/toluene	**13′**	0
8	**10a**	C/rt/benzene	**12′**	83
9	**10a**	C/rt/hexane	**12′**	75
10	**10a**	C/rt/MeCN	**12′**	40
11	**10a**	C/rt/THF	**12′**	33
12	**10a**	C/rt/CH_2Cl_2	**12′**	9
13	**10b**	C/rt/toluene	**12′**	88

[a] The radical reaction mixture was directly treated with TBAF, the product of which was isolated as a 3,5-dinitrobenzoate. [b] A: $(Bu_3Sn)_2$ (1.0 equiv), AIBN (0.6 equiv). B: $(Bu_3Sn)_2$ (0.1 equiv), *hν*. C: Et_3B (0.3 equiv). D: $(Bu_3Sn)_2$ (0.3 equiv), V70 (0.3 equiv).

SCHEME 5

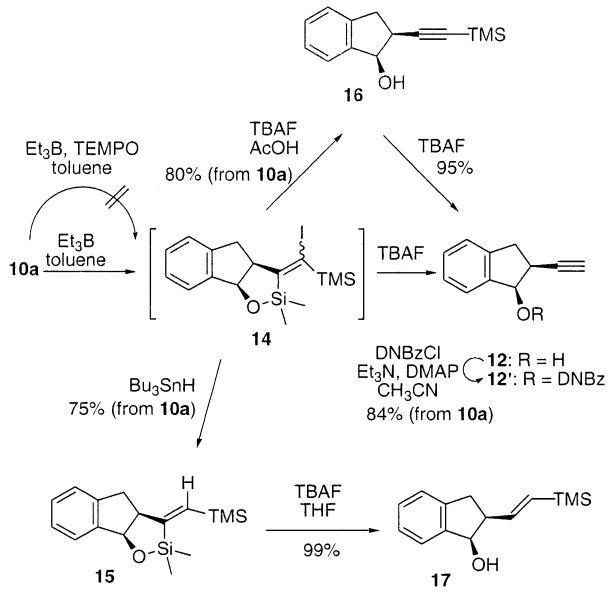


The effect of the solvent on the reaction was next examined. As shown in entries 3 and 8−12, nonpolar solvents, such as benzene, toluene, or hexane, were suitable for the reaction, while the yield decreased when a relatively polar solvent, MeCN, THF, or CH_2Cl_2, was used.

On the basis of these experiments, we confirmed that the best procedure was that used in entry 3, namely, treatment of an iodohydrin-derived substrate with 0.3 equiv of Et_3B at room temperature in toluene under argon.[30]

We next examined the reaction using the EDMS group to compare it with the TEDMS group as the tether. The EDMS ether **10b**, which was prepared by treating **8** with EDMS chloride (EDMS−Cl)[31] and Et_3N in THF, was subjected to the reaction under the best reaction conditions used in entry 3. The reaction afforded the desired ethynyl product **12′** in 88% yield (entry 13). Thus, the EDMS group was shown to be as effective as the TEDMS group.

SCHEME 6



Investigation of the Reaction Pathway. The reaction pathway was investigated with the iodoindanol substrate **10a**. In the above experiments, the substrate **10a** was effectively converted into *cis*-2-ethynylindanol **12** (**12′**), which corresponded to the expected atom-transfer radical cyclization and subsequent elimination product shown in Scheme 3. When **10a** was treated under the best conditions noted above with Et_3B but in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), the radical reaction did not proceed, and the starting material **10a** was recovered in 88% yield (Scheme 6). Thus, it was confirmed that the radical reaction process is involved in the reaction pathway, as expected.

We next tried to isolate the atom-transfer radical cyclization product **14**; however, it was too labile to be isolated. Therefore, after the radical reaction of **10a** with Et_3B, the crude product was derivatized. The reductive treatment of the radical reaction mixture with Bu_3SnH afforded the stable (*Z*)-*exo*-methylene product **15**,[27] which was isolated in 75% yield from **10a**. On the other hand, when TBAF (1 equiv) and AcOH (0.35 equiv) were added to the radical reaction mixture, *cis*-2-(2-trimethylsilylethynyl)indanol (**16**) was isolated in 80% yield from **10a**. It is reasonable to assume that the two products **15** and **16** were formed from the expected atom-transfer product **14** by its radical reduction and elimination reaction, respectively.

The reactivity of compounds **15** and **16** to fluoride ion was next examined. Treatment with 2.5 equiv of TBAF quantitatively converted **15** into *cis*-2-[(*E*)-2-trimethylsilylvinyl]indanol (**17**)[32] and **16** into *cis*-2-ethynylindanol (**12**), respectively. These results suggest that elimination of the atom transfer product **14** forms 2-(2-trimethylsilylethynyl)indanol (**16**), the trimethylsilyl group of which was subsequently removed to furnish the *cis*-2-ethynylindanol (**12**).

(28) The cis-stereochemistry was determined by NOE experiments: see Experimental Section.

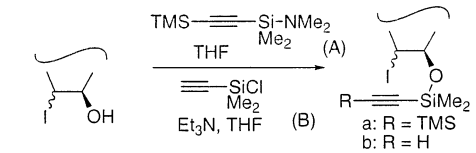
(29) When 0.1−0.5 equiv of Et_3B was used under argon, it effectively promoted the atom-transfer radical cyclization reactions of **10a**.

(30) When the reaction was carried out under oxygen or air, the yield significantly decreased.

(31) Shinohara, N.; Arai, M.; Ichinohe, S. JP-52065226, 1977 (*Chem. Abstr.* **1977**, *87*, P 135905r).

(32) The *E*-configuration was determined by the ^1H NMR coupling constant: see Experimental Section.

TABLE 2. Preparation of the Reaction Substrates



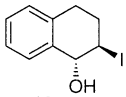
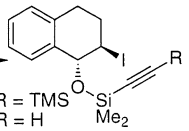
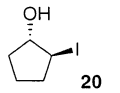
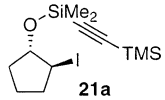
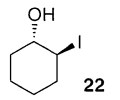
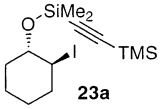
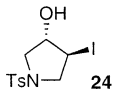
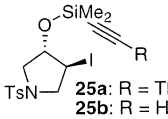
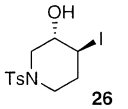
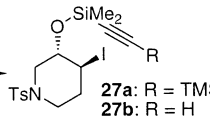
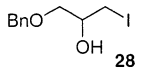
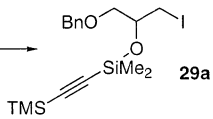
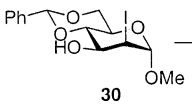
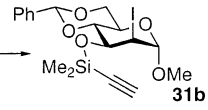
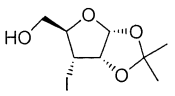
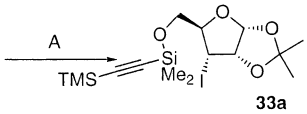
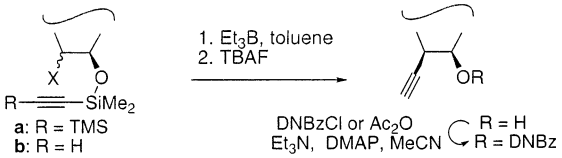
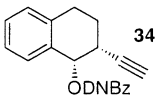
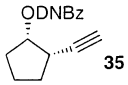
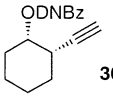
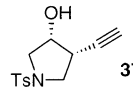
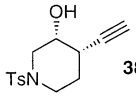
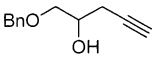
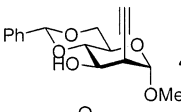
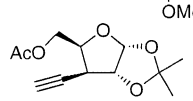
substrate	method	product	yield
 **18**	A or B	 **19a**: R = TMS **19b**: R = H	67% 70%
 **20**	A	 **21a**	78%
 **22**	A	 **23a**	90%
 **24**	A or B	 **25a**: R = TMS **25b**: R = H	63% quant.
 **26**	A or B	 **27a**: R = TMS **27b**: R = H	77% quant.
 **28**	A	 **29a**	63%
 **30**	B	 **31b**	90%
 **32**	A	 **33a**	quant.

TABLE 3. Atom-Transfer Radical Cyclization and Subsequent Elimination Reaction of Various Substrates[a]



entry	substrate	product[b]	yield
1 2	**19a** **19b**	 **34**	83% 86%
3	**21a**	 **35**	33%
4	**23a**	 **36**	36%
5 6	**25a** **25b**	 **37**	80% 80%
7 8	**27a** **27b**	 **38**	55% 68%
9[c]	**29a**	 **39**	18%
10	**31b**	 **40**	85%
11[d]	**33a**	 **41**	31%

[a] The substrate (0.10 mmol) was successively treated with Et_3B (0.30 equiv) and then with TBAF (2.5 equiv) in toluene at room temperature, and the product was purified by silica gel column chromatography. [b] The product was isolated after its conversion into the corresponding 3,5-dinitrobenzoate (entries 1−4) or acetate (entry 11). [c] The radical reaction was carried out with 0.60 equiv of Et_3B. [d] The radical reaction was carried out at 50 °C.

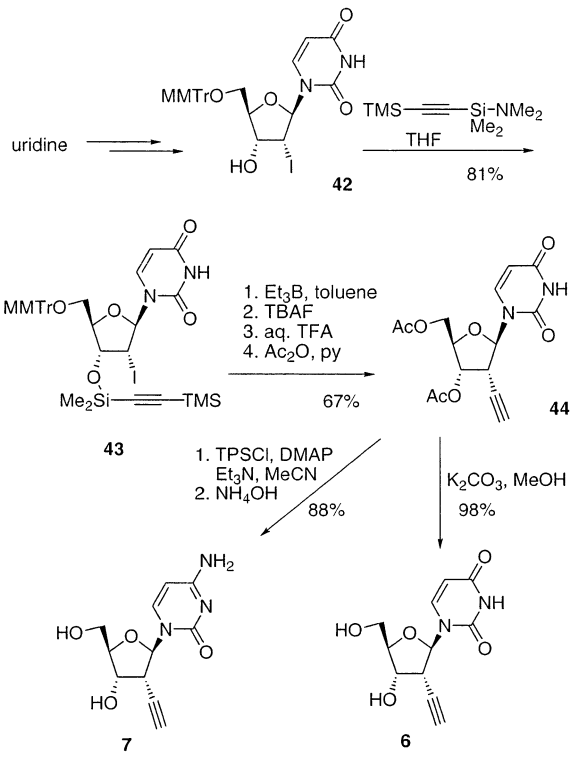
On the basis of these experiments, we concluded that the reaction pathway is an atom-transfer radical cyclization and subsequent elimination via intermediates **14** (**IV**) and **16** (**V**), which is identical with what we hypothesized above.

Ethynyl-Introduction Reaction with Various Substrates. With the above encouraging results in mind, we then examined the reaction using the TEDMS or EDMS ethers of a variety of iodohydrins as reaction substrates. The substrates were prepared according to the above methods, as summarized in Table 2. The reactions were carried out according to the best method confirmed by the above experiments, i.e., the procedure identical with that of entry 3 in Table 1. The products were isolated after purification by silica gel column chromatography, and the results are shown in Table 3.

We first performed the reaction with the TEDMS ether of *trans*-2-iodotetrahydronaphthol (**19a**), which corresponds to the ring-expanded derivative of the model indanol substrate **10a**. The reaction successfully proceeded to give the desired ethynyl product **34** in 83% yield (entry 1). When the corresponding EDMS ether **19b** was used as the substrate, the product **34** was also obtained in high yield (86%, entry 2).

Reactions with more simplified monocyclic substrates, the TEDMS ethers **21a** and **23a** of 2-iodo-cyclopentanol and 2-iodo-cyclohexanol, were next examined. Although the TLC analysis suggested that both of the reactions seemed to proceed effectively like those of the above indanol and tetrahydronaphthol substrates, the 2-ethynyl products **35** and **36** were obtained in only moderate yields (entries 3 and 4). The comparatively low isolated yields might be explained by the volatility of the ethynylcycloalkanol products. Reactions with similar simplified five- and six-membered-ring substrates, i.e., pyrrolidine and piperidine derivatives **25a**, **25b**, **27a**, and **27b**, however, afforded the corresponding ethynyl products in relatively good yields (entries 5−8), lending more support

SCHEME 7



to this presumption. Thus, it appears that the expected reaction sequence occurs in both five- and six-membered-ring iodohydrin substrates.

When the reaction was applied to the acyclic iodohydrin substrate **29a**, the expected ethynyl product **39** was also obtained. However, the radical reaction was rather slow and the yield of the product **39** was low. It seems that abstraction of the iodine atom of the substrate **29a** by the cyclized radical (**III** in Scheme 3) is unfavorable because it results in producing the relatively unstable primary radical in this case.

The reaction was finally applied to sugar derivatives. Thus, treatment of the 3′-EDMS ether of the 2-deoxy-2-iodo-D-mannoside **31b** following the same procedure furnished the expected 2-ethynyl product **40** in 85% yield. The results demonstrate that *cis*-halohydrin can also be the effective substrate in this reaction. However, a similar reaction of 3-iodo-D-ribosyl substrate **33a** having the TEDMS group at the 5-hydroxyl gave the desired product **41**, the ethynyl group of which was introduced at the γ-cis position to the 5′-hydroxyl, in only 31% yield. This may be because the 6-*exo* radical cyclization did not occur so readily.

As described, we have successfully developed an efficient radical method, using the TEDMS or EDMS ethers of cyclic iodohydrines as substrates, for introducing an ethynyl group at the β-cis position to the hydroxyl. **Synthesis of 2′-Deoxy-2′-*C*-ethynyluridine and 2′-Deoxy-2′-*C*-ethynylcytidine.** We tried to synthesize the targets 2′-deoxy-2′-*C*-ethynyluridine (**6**) and 2′-deoxy-2′-*C*-ethynylcytidine (**7**) using the developed reaction as the key step (Scheme 7). The 2′-deoxy-2′-iodouridine derivative **42**, readily prepared from uridine via 2,2′-anhydrouridine,[5] was treated as in the above-mentioned procedure with TEDMS−NMe_2 to give the corresponding 3′-*O*-TEDMS derivative **43**, the substrate for the key radical reaction. When **43** was subjected to the best procedure as in entry 3 in Table 1, the expected reaction sequence produced the desired 2′-*C*-ethynylnucleoside. After removal of the monomethoxytrityl (MMTr) group and subsequent treatment with Ac_2O in pyridine, 3′,5′-di-*O*-acetyl-2′-deoxy-2′-*C*-ethynyluridine (**44**) was isolated in 67% yield from the substrate **43**, as expected. Removal of the acetyl groups with K_2CO_3/MeOH finally produced the target 2′-deoxy-2′-*C*-ethynyluridine (**6**). Another target, the corresponding cytidine congener **7**, was obtained in 88% yield by treating **44** with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl), Et_3N, and DMAP in MeCN followed by NH_4OH.

Conclusion. We have developed an efficient method for introducing an ethynyl group via an atom-transfer radical cyclization reaction with an EDMS or a TEDMS group as a temporary connecting tether followed by a fluoride ion-promoted elimination reaction. The method was shown to be applicable to the introduction of an ethynyl group in various five- and six-membered-ring iodohydrins. 2′-Deoxy-2′-*C*-ethynyluridine (**6**) and 2′-deoxy-2′-*C*-ethynylcytidine (**7**), newly designed as potential antimetabolites, were effectively synthesized by using this reaction as the key step. This would be the first example in which a radical reaction was used for introducing an ethynyl group.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded at 270 and 400 MHz (^{1}H) and at 100 MHz (^{13}C), and are reported in ppm downfield from Me_4Si. Mass spectra were obtained by electron ionization (EI) or the fast atom bombardment (FAB) method. Thin-layer chromatography was performed on Merck coated plate $60F_{254}$. Silica gel chromatography was performed with Merck silica gel 5715 or 9385 (neutral). Reactions were carried out under an argon atmosphere.

***trans*-2-Iodo-1-[(trimethylsilyl)ethylnyldimethylsiloxy]-indane (10a).** A solution of **8** (757 mg, 2.9 mmol) and dimethyl[(trimethylsilylethynyl)dimethylsilyl]amine (TEDMS−NMe_2, 805 μL, 3.2 mmol) in toluene (15 mL) was stirred at room temperature for 3 h and then evaporated. The residue was purified by column chromatography (neutral SiO_2, 0−3% Et_2O in hexane) to give **10a** (997 mg, 83%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.20 (m, 4 H), 5.56 (d, 1 H, J = 5.3 Hz), 4.30 (dt, 1 H, J = 5.3, 7.0 Hz), 3.64 (dd, 1 H, J = 7.0, 16.4 Hz), 3.30 (dd, 1 H, J = 7.0, 16.4 Hz), 0.43 (s, 3 H), 0.37 (s, 3 H), 0.22 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.30, 140.77, 128.38, 127.02, 124.55, 124.08, 115.50, 110.83, 85.68, 42.80, 29.97, 1.34, 1.00, −0.04; LRMS (EI) m/z 399 (M^+ − CH_3). Anal. Calcd for $C_{16}H_{23}IOSi_2$: C, 46.37; H, 5.59. Found: C, 46.46; H, 5.66.

***trans*-2-iodo-1-(ethynyldimethylsiloxy)indane (10b).** A solution of **8** (260 mg, 1.0 mmol), Et_3N (307 μL, 2.2 mmol), and ethynyldimethylchlorosilane (EDMS−Cl, 279 μL, 2.0 mmol) in toluene (10 mL) was stirred at room temperature for 3 h, and then evaporated. The residue was partitioned between AcOEt and aqueous saturated $Na_2S_2O_3$, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (neutral SiO_2, 0−5% AcOEt in hexane) to give **10b** (243 mg, 71%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.19 (m, 4 H), 5.57 (d, 1 H, J = 5.6 Hz), 4.28 (dt, 1 H, J = 5.6, 7.2 Hz), 3.62 (dd, 1 H, J = 7.2, 16.4 Hz), 3.30 (dd, 1 H, J = 7.2, 16.4 Hz), 2.56 (s, 1 H), 0.46 (s, 3 H), 0.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.99, 140.54, 128.25, 126.95, 124.09, 123.91, 94.19, 87.38, 85.68, 42.56, 29.53, 1.24, 0.75;

LRMS (EI) *m*/*z* 342 (M^+). Anal. Calcd for $C_{13}H_{15}IOSi$: C, 45.62; H, 4.42. Found: C, 45.62; H, 4.52.

***trans*-1-Phenylseleno-2-[(trimethylsilyl)ethynyldimethylsiloxy]indane (11a).** Compound **11a** (992 mg, 45%) was obtained as a colorless liquid from **9** (1.45 g, 5.0 mmol) as described above for the synthesis of **10a**, after purification by column chromatography (neutral SiO_2, 0−2% AcOEt in hexane): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.55−7.17 (m, 9 H), 4.76−4.74 (m, 2 H), 3.22 (dd, 1H, J = 5.9, 15.8 Hz), 2.88 (d, 1 H, J = 15.8 Hz), 0.21 (s, 9 H), 0.14 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.17, 140.83, 134.34, 129.48, 128.80, 127.59, 127.46, 126.62, 125.40, 124.83, 114.68, 111.22, 80.22, 54.04, 40.46, 0.47, −0.01; LRMS (EI) *m*/*z* 444 (M^+). Anal. Calcd for $C_{22}H_{28}OSeSi_2$: C, 59.57; H, 6.36. Found: C, 59.63; H, 6.39.

1,2,3,4-Tetrahydro-2-iodo-1-[(trimethylsilyl)ethynyldimethylsiloxy]naphthalene (19a). Compound **19a** (115 mg, 67%) was obtained as a colorless liquid from **18** (110 mg, 0.40 mmol) as described above for the synthesis of **10a**, after purification by column chromatography (neutral SiO_2, 0−2% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.13 (m, 4 H), 5.19 (d, 1 H, J = 2.9 Hz), 4.72 (m, 1 H), 3.00 (m, 1 H), 2.85 (m, 1 H), 2.32 (m, 1 H), 2.06 (m, 1 H), 0.33 (s, 3 H), 0.32 (s, 3 H), 0.25 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.07, 134.21, 130.38, 128.72, 127.97, 136.05, 115.72, 110.55, 74.75, 33.60, 27.61, 26.61, 1.07, 0.93; LRMS (EI) *m*/*z* 413 ($M^+ - CH_3$). Anal. Calcd for $C_{17}H_{25}IOSi_2$: C, 47.66; H, 5.88. Found: C, 47.87; H, 5.96.

1,2,3,4-Tetrahydro-2-iodo-1-(ethynyldimethylsiloxy)naphthalene (19b). Compound **19b** (149 mg, 70%) was obtained as a colorless liquid from **18** (164 mg, 0.60 mmol) as described above for the synthesis of **10b**, after purification by column chromatography (neutral SiO_2, 0−5% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.12 (m, 4 H), 5.20 (d, 1 H, J = 3.3 Hz), 4.67 (m, 1 H), 2.99 (m, 1 H), 2.85 (m, 1 H), 2.60 (s, 1 H), 2.33 (m, 1 H), 2.08 (m, 1 H), 0.35 (s, 3 H), 0.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.06, 133.14, 129.20, 127.71, 127.02, 125.09, 93.41, 86.47, 74.05, 32.41, 26.65, 25.89, 0.00, −0.07; LRMS (EI) *m*/*z* 356 (M^+). Anal. Calcd for $C_{14}H_{17}IOSi$: C, 47.20; H, 4.81. Found: C, 47.16; H, 4.89.

***trans*-2-Iodo-1-[(trimethylsilyl)ethynyldimethylsiloxy]cyclopentane (21a).** Compound **21a** (285 mg, 78%) was obtained as a colorless liquid from **20** (212 mg, 1.0 mmol) as described above for the synthesis of **10a**, after purification by column chromatography (neutral SiO_2, 0−3% ether in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (m, 1 H), 4.19 (m, 1 H), 2.35 (m, 1 H), 2.18 (m, 1 H), 2.03 (m, 1 H), 1.83 (m, 2 H), 1.64 (m, 1 H), 0.27 (s, 3 H), 0.25 (s, 3 H), 0.21 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.88, 110.72, 83.01, 35.83, 34.59, 31.91, 0.67, 0.57, 0.01; LRMS (EI) *m*/*z* 366 (M^+). Anal. Calcd for $C_{12}H_{23}OSi_2$: C, 39.34; H, 6.33. Found: C, 39.47; H, 6.34.

***trans*-2-Iodo-1-[(trimethylsilyl)ethynyldimethylsiloxy]cyclohexane (23a).** Compound **23a** (1.36 g, 90%) was obtained as a colorless liquid from **22** (0.90 g, 4.0 mmol) as described above for the synthesis of **10a,** after purification by column chromatography (neutral SiO_2, 0−5% ether in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (ddd, 1 H, J = 4.1, 8.7, 10.5 Hz), 3.89 (dt, 1 H, J = 4.1, 12.6 Hz), 2.41 (m, 1 H), 2.22 (m, 1 H), 1.97 (m, 1 H), 1.80 (m, 1 H), 1.52 (m, 1 H), 1.45−1.23 (m, 3 H), 0.35 (s, 3 H), 0.28 (s, 3 H), 0.19 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.68, 111.64, 76.65, 39.82, 37.71, 34.37, 26.85, 23.48, 1.21, 0.91, −0.12; LRMS (EI) *m*/*z* 380 (M^+). Anal. Calcd for $C_{13}H_{25}IOSi_2$: C, 41.04.; H, 6.62. Found: C, 41.15; H, 6.50.

***trans*-4-Iodo-1-tosyl-3-[(trimethylsilyl)ethynyldimethylsiloxy]pyrrolidine (25a).** Compound **25a** (131 mg, 63%) was obtained as a white solid from **24** (147 mg, 0.40 mmol) as described above for the synthesis of **10a**, after purification by column chromatography (neutral SiO_2, 6% AcOEt in hexane): mp 77−78 °C (white crystals from hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.73 (d, 2 H, J = 8.6 Hz), 7.31 (d, 2 H, J = 8.6 Hz), 4.51 (m, 1 H), 4.09 (m, 1 H), 4.02 (dd, 1 H, J = 5.9, 11.2 Hz), 3.87 (dd, 1 H, J = 4.6, 11.2 Hz), 3.71 (dd, 1 H, J = 2.0, 11.2 Hz), 3.38 (d, 1 H, J = 11.2 Hz), 2.42 (s, 3 H), 0.20 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.35, 133.73, 129.42, 127.51, 127.41, 116.33, 109.32, 79.30, 55.83, 53.32, 24.63, 21.65, 0.31, 0.17, −0.08; LRMS (FAB, positive) *m*/*z* 522 (MH^+). Anal. Calcd for $C_{18}H_{28}INO_3SSi_2$: C, 41.45; H, 5.41; N, 2.69. Found: C, 41.39; H, 5.37; N, 2.61.

***trans*-3-Ethynyldimethylsiloxy-4-iodo-1-tosylpyrrolidine (25b).** Compound **25b** (92 mg, quant.) was obtained as a white solid from **24** (73 mg, 0.20 mmol) as described above for the synthesis of **10b**, after usual water workup: mp 95−96 °C (white crystals from hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 2 H, J = 8.3 Hz), 7.32 (d, 2 H, J = 8.3 Hz), 4.50 (m, 1 H), 4.05−3.99 (m, 2 H), 3.87 (dd, 1 H, J = 4.3, 11.1 Hz), 3.71 (dd, 1 H, J = 5.5, 15.1 Hz), 3.36 (dd, 1 H, J = 2.1, 11.1 Hz), 2.50 (s, 1 H), 2.43 (s, 3 H), 0.17 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.36, 133.67, 129.42, 127.46, 94.70, 86.38, 79.30, 55.80, 53.22, 24.24, 21.62, 0.21; LRMS (FAB, positive) *m*/*z* 450 (MH^+). Anal. Calcd for $C_{15}H_{20}INO_3SSi$: C, 40.09; H, 4.49; N, 3.12. Found: C, 40.14; H, 4.49; N, 3.12.

***trans*-4-Iodo-1-tosyl-3-[(trimethylsilyl)ethynyldimethylsiloxy]piperidine (27a).** Compound **27a** (140 mg, 77%) was obtained as a white solid from **26** (114 mg, 0.30 mmol) as described above for the synthesis of **10a**, after purification by column chromatography (neutral SiO_2, 4% AcOEt in hexane): mp 110.5−112 °C (white needles from hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, 2 H, J = 8.3 Hz), 7.33 (d, 2 H, J = 8.3 Hz), 4.01 (m, 1 H), 3.95 (ddd, 1 H, J = 1.7, 4.4, 11.7 Hz), 3.80 (m, 1 H), 3.38 (ddd, 1 H, J = 2.8, 4.1, 11.7 Hz), 2.53−2.45 (m, 2 H), 2.44 (s. 3H), 2.37 (ddd, 1 H, J = 4.4, 7.5, 23.9 Hz), 2.18 (ddd, 1 H, J = 4.1, 10.4, 23.9 Hz), 0.36 (s, 3 H), 0.29 (s, 3 H), 0.24 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.50, 133.32, 129.58, 127.41, 116.01, 109.86, 72.97, 50.95, 46.63, 35.05, 31.65, 21.68, 0.92, 0.80, −0.07; LRMS (FAB, positive) *m*/*z* 536 (MH^+). Anal. Calcd for $C_{19}H_{30}INO_3SSi_2$: C, 42.61; H, 5.65; N, 2.62. Found: C, 42.55; H, 5.56; N, 2.50.

***trans*-3-Ethynyldimethylsiloxy-4-iodo-1-tosylpiperidine (27b).** Compound **27b** (94 mg, quant.) was obtained as a white solid from **26** (76 mg, 0.20 mmol) as described above for the synthesis of **10b**, after purification by the only partition: mp 104−105 °C (white needles from hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 2 H, J = 8.4 Hz), 7.33 (d, 2 H, J = 8.4 Hz), 4.01 (m, 1 H), 3.95 (ddd, 1 H, J = 2.0, 4.2, 11.7 Hz), 3.78 (ddd, 1 H, J = 4.4, 8.2, 10.7 Hz), 3.41 (m, 1 H), 2.56 (s, 1 H), 2.53−2.35 (m, 3 H), 2.44 (s, 3 H), 2.22 (ddd, 1 H, J = 4.2, 10.7, 24.5 Hz), 0.40 (s, 3 H), 0.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.40, 133.18, 129.44, 94.53, 86.76, 73.07, 50.90, 46.50, 35.15, 31.30, 21.50, 0.66, 0.58; LRMS (FAB, positive) *m*/*z* 464 (MH^+). Anal. Calcd for $C_{16}H_{22}INO_3SSi$: C, 41.47; H, 4.79; N, 3.02. Found: C, 41.76; H, 4.88; N, 2.81.

1-Benzyloxy-3-iodo-2-[(trimethylsilyl)ethynyldimethylsiloxy]propane (29a). Compound **29a** (290 mg, 65%) was obtained as a colorless liquid from **28** (292 mg, 1.0 mmol) as described above for the synthesis of **10a** with TEDMS−NMe_2 (303 μL, 1.0 mmol) at 50 °C, after purification by column chromatography (neutral SiO_2, 0−4% Et_2O in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5 H), 4.56 (s, 2 H), 3.95 (m, 1H), 3.62 (dd, 1 H, J = 5.3, 9.9 Hz), 3.53 (dd, 1 H, J = 5.3, 9.9 Hz), 3.43 (dd, 1 H, J = 5.9, 10.6 Hz), 3.33 (dd, 1 H, J = 5.3, 10.6 Hz), 0.32 (s, 3 H), 0.27 (s, 3 H), 0.19 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.83, 128.22, 127.54, 115.10, 110.47, 73.43, 72.79, 71.50, 10.08, 0.87, 0.83, −0.05; LRMS (ESI) *m*/*z* 469 (MNa^+). Anal. Calcd for $C_{17}H_{27}IO_2Si_2$: C, 45.73; H, 6.10. Found: C, 45.78; H, 6.03.

Methyl 2-Deoxy-2-iodo-3-*O*-ethynyldimethylsilyl-4,6-*O*-benzylidene-α-D-mannopyranoside (31b). Compound **31b** (107 mg, 90%) was obtained as a white syrup from **30** (98 mg, 0.25 mmol) as described above for the synthesis of **10b** with EDMS−Cl (88 μL, 0.63 mmol), pyridine (57 μL, 0.70 mmol) instead of Et_3N, and THF (2.5 mL) as a solvent, after purification by the only partition: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.34 (m, 5 H), 5.59 (s, 1 H), 5.13 (s, 1 H), 4.53 (d, 1 H,

J = 4.5 Hz), 4.25 (dd, 1 H, J = 3.4, 9.3 Hz), 3.99−3.84 (m, 3 H), 3.55 (dd, 1 H, J = 4.5, 8.8 Hz), 3.38 (s, 3 H), 2.54 (s, 1 H), 0.32 (s, 3 H), 0.28 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.98, 128.53, 127.74, 125.81, 103.57, 101.44, 93.50, 87.25, 80.33, 68.46, 67.30, 64.30, 54.98, 37.23, 0.71, 0.47; LRMS (EI) m/z 474 (M^+). Anal. Calcd for $C_{18}H_{23}IO_5Si$: C, 45.58; H, 4.89. Found: C, 45.87; H, 5.06.

3-Deoxy-5-*O*-ethynyldimethylsilyl-3-iodo-1,2-*O*-(1-methylethylidene)-α-D-ribofuranose (33a). Compound **33a** (116 mg, quant.) was obtained as a colorless viscous oil from **32** (90 mg, 0.3 mmol) as described above for the synthesis of **10a**, after purification by column chromatography (neutral SiO_2, 5−15% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (d, 1 H, J = 3.6 Hz), 4.63 (dd, 1 H, J = 3.6, 4.3 Hz), 4.17 (dt, 1 H, J = 2.3, 10.4 Hz), 4.09 (dd, 1 H, J = 2.3, 12.2 Hz), 4.00 (m, 1 H), 3.96 (dd, 1 H, J = 2.3, 12.2 Hz), 2.47 (s, 1 H), 1.56 (s, 3 H), 1.38 (s, 3 H), 0.32 (s, 3 H), 0.31 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.22, 103.26, 93.45, 87.19, 83.00, 80.70, 59.82, 26.52, 26.43, 19.92, 0.02, −0.23; HRMS (FAB, positive) calcd for $C_{12}H_{20}IO_4Si$ 383.0176, found 383.0171 (MH^+).

Bu_3SnH-Reduction Product 15. To a solution of **10a** (124 mg, 0.3 mmol) in toluene (3 mL) was added dropwise Et_3B (1.0 M solution in hexane, 90 μL, 0.090 mmol) under argon atmosphere, and the mixture was stirred at room temperature for 2 h. After addition of Bu_3SnH (97 μL, 0.36 mmol), the resulting mixture was stirred at room temperature for an additional 2 h. The resulting mixture was evaporated, and the residue was purified by column chromatography (SiO_2, 0−3% AcOEt in hexane) to give **15** (65 mg, 75%) as a colorless liquid: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.50−7.20 (m, 4 H, Ar), 6.67 (d, 1 H, −C=CH, J = 2.0 Hz), 5.48 (d, 1 H, H-1, J = 5.9 Hz), 3.41 (m, 1 H, H-2), 3.24 (dd, 1 H, H-3a, J = 9.2, 16.5 Hz), 2.93 (dd, 1 H, H-3b, J = 5.9, 16.5 Hz), 0.41 (s, 3 H, Si−CH_3), 0.19 (s, 3 H, Si−CH_3), 0.14 (s, 9 H, TMS); NOE (400 MHz, $CDCl_3$), irradiated H-2, observed H-1 (9.5%), H-3a (4.9%), and irradiated −C=C*H*TMS, observed H-2 (5.6%), H-3b (2.8%); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.52, 143.95, 142.47, 128.29, 126.64, 125.06, 124.54, 83.16, 55.19, 39.17, 1.73, 1.31, 0.12; LRMS (EI) m/z 288 (M^+). Anal. Calcd for $C_{16}H_{24}OSi_2$: C, 66.60; H, 8.38. Found: C, 66.77; H, 8.54.

***cis*-2-[*E*-2-(Trimethylsilyl)vinyl]-1-indanol (17).** A mixture of **15** (65 mg, 0.225 mmol) and TBAF (1.0 M solution in THF, 563 μL, 0.56 mmol) in THF (2 mL) was stirred at room temperature for 1 h and then evaporated. The residue was purified by column chromatography (SiO_2, 3−8% AcOEt in hexane) to give **17** (52 mg, 99%) as a white solid: mp 56−58 °C (white crystals from hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.22 (m, 4 H, Ar), 6.14 (dd, 1 H, −CH=C, J = 7.0, 18.8 Hz), 5.94 (dd, 1 H, −C=CH, J = 0.9, 18.8 Hz), 5.09 (dd, 1 H, H-1, J = 5.6, 5.9 Hz), 3.17 (m, 1 H, H-2), 3.01 (m, 2 H, H-3a,3b), 1.65 (d, 1 H, OH-1, J = 5.6 Hz), 0.09 (s, 9 H, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.06, 142.39, 134.46, 128.33, 126.63, 124.82, 124.66, 76.88, 51.93, 35.28, −0.96; LRMS (EI) m/z 214 ($M^+ - H_2O$). Anal. Calcd for $C_{14}H_{20}OSi$: C, 72.36; H, 8.67. Found: C, 72.40; H, 8.83.

***cis*-2-(Trimethylsilyl)ethynyl-1-indanol (16).** To a solution of substrate **8a** (41 mg, 0.10 mmol) in toluene (1 mL) was added dropwise Et_3B (1.0 M solution in hexane, 30 μL, 0.03 mmol) under argon atmosphere, and the mixture was stirred at room temperature for 2 h. After addition of a mixture of TBAF (1.0 M solution in THF, 100 μL, 0.10 mmol) and AcOH (2 μL, 0.035 mmol), the resulting mixture was stirred at room temperature for an additional 1 h, and then evaporated. The residue was purified by column chromatography (SiO_2, 0−5% AcOEt in hexane) to give **16** (19 mg, 80%) as a white solid: mp 98−100 °C (white needles from hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.47−7.23 (m, 4 H), 5.07 (dd, 1 H, J = 6.1, 5.6 Hz), 3.41 (m, 1 H), 3.14 (m, 2 H), 2.47 (d, 1 H, J = 5.6 Hz), 0.17 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.37, 141.37, 128.61, 126.89, 125.16, 124.65, 104.53, 89.48, 75.25, 39.14, 37.11, 0.28; LRMS (FAB, positive) m/z 253 (MNa^+). Anal. Calcd for $C_{14}H_{18}OSi$: C, 72.99; H, 7.88. Found: C, 72.69; H, 7.91.

***cis*-2-Ethynyl-1-indanol (12).** A mixture of **16** (23 mg, 0.10 mmol) and TBAF (1.0 M solution in THF, 120 μL, 0.12 mmol) in THF (1 mL) was stirred at room temperature for 1 h. The mixture was evaporated, and the residue was purified by column chromatography (SiO_2, 5−10% AcOEt in hexane) to give **12** (15 mg, 95%) as a white solid: mp 80−81 °C (white needles from hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.46−7.22 (m, 4 H), 5.11 (m, 1 H), 3.39 (m, 1 H), 3.20 (dd, 1 H, J = 5.9, 15.8 Hz), 3.14 (dd, 1 H, J = 7.9, 15.8 Hz), 2.39 (br s, 1H), 2.23 (d, 1 H, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.44, 141.06, 128.69, 127.04, 124.94, 124.73, 82.75, 75.66, 72.40, 38.16, 36.84; LRMS (FAB, positive) m/z 158 (M^+). Anal. Calcd for $C_{11}H_{10}O$: C, 83.51; H, 6.37. Found: C, 83.43; H, 6.52.

General Procedure for Radical Atom-Transfer Reaction with Et_3B (Tables 1 and 3). To a solution of a substrate (0.10 mmol) in toluene (1 mL) was added dropwise Et_3B (1.0 M solution in hexane, 30 μL, 0.030 mmol) under argon atmosphere, and the mixture was stirred at room temperature for 2 h. After addition of TBAF (1.0 M solution in THF, 250 μL, 0.25 mmol), the resulting mixture was stirred at room temperature for an additional 2 h and then the solvent was evaporated. To the residue was added AcOEt, and the insoluble material was filtered off. The filtrate was evaporated, and the residue was treated according to the procedure as described below.

***cis*-1-(3,5-Dinitrobenzoyloxy)-2-ethynylindane (12′).** After the treatment of **10a** (41 mg, 0.10 mmol) or **10b** (34 mg, 0.10 mmol) according to the above general procedure, a mixture of the resulting residue, DNBzCl (35 mg, 0.15 mmol), Et_3N (28 μL, 0.2 mmol), and DMAP (2 mg, 0.02 mmol) in MeCN (1 mL) was stirred at room temperature for 3 h, and then evaporated. The residue was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 3−6% AcOEt in hexane) to give **12′** (30 mg, 84% from **10a**, or 31 mg, 88% from **10b**) as a white solid: mp 154−155 °C (colorless crystals from AcOEt/hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.21−9.18 (m, 3 H, DNBz), 7.57−7.26 (m, 4 H, Ar), 6.50 (d, 1 H, H-1, J = 5.9 Hz), 3.60 (m, 1 H, H-2), 3.39 (m, 2 H, H-3a,3b), 2.18 (d, 1 H, −C≡CH, J = 2.6 Hz); NOE (400 MHz, $CDCl_3$), irradiated H-2, observed H-1 (10.9%), and irradiated −C≡C*H*, observed DNBz (1.3%); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.92, 148.40, 142.83, 137.98, 133.98, 130.12, 129.48, 127.39, 126.36, 124.83, 122.24, 81.45, 79.49, 71.93, 37.95, 35.65; LRMS (EI) m/z 140 (M^+ − DNBzOH). Anal. Calcd for $C_{18}H_{12}N_2O_6$: C, 61.37; H, 3.43; N, 7.95. Found: C, 61.33; H, 3.51; N, 7.87.

1,2,3,4-Tetrahydro-1-(3,5-dinitrobenzoyloxy)-2-ethynylnaphthalene (34). After the treatment of **19a** (43 mg, 0.10 mmol) or **19b** (36 mg, 0.10 mmol) according to the above general procedure, the product was converted into the corresponding dinitrobenzoate as described above for the synthesis of **12′**. The purification was carried out by column chromatography (SiO_2, 2−5% AcOEt in hexane) to give **34** (30 mg, 83% from **19a**, or 32 mg, 86% from **19b**) as a white solid: mp 170−171 °C (white crystals from hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22−9.17 (m, 3 H), 7.42−7.20 (m, 4 H), 6.50 (d, 1 H, J = 3.8 Hz), 3.18−3.10 (m, 2 H), 2.91 (m, 1 H), 2.34 (m, 1 H), 2.22 (m, 1 H), 2.06 (d, 1 H, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.94, 148.40, 136.51, 133.90, 131.77, 129.86, 129.49, 129.13, 126.48, 122.26, 82.77, 72.53, 71.22, 31.89, 27.88, 24.92; LRMS (EI) m/z 366 (M^+). Anal. Calcd for $C_{19}H_{14}N_2O_6$: C, 62.30; H, 3.85; N, 7.65. Found: C, 62.25; H, 4.02; N, 7.53.

***cis*-1-(3,5-Dinitrobenzoyloxy)-2-ethynylcyclopentane (35).** After the treatment of **21a** (37 mg, 0.10 mmol) according to the above general procedure, the product was converted to the corresponding dinitrobenzoate as described above for the synthesis of **12′**. Purification was carried out by column chromatography (SiO_2, 0−8% AcOEt) to give **35** (10 mg, 33%)

as a pale brown solid: mp 117−118 °C (pale brown crystals from hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24−9.19 (m, 3 H), 5.55 (m, 1 H), 3.00 (m, 1 H), 2.20 (m, 2 H), 2.09 (d, 1 H, J = 2.6 Hz), 2.07−1.96 (m, 3 H), 1.73 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.74, 148.41, 134.11, 129.34, 122.17, 82.31, 78.74, 71.33, 35.81, 31.53, 31.50, 22.46; LRMS (EI) m/z 304 (M^+). Anal. Calcd for $C_{14}H_{12}N_2O_6$: C, 55.27; H, 3.98; N, 9.21. Found: C, 55.10; H, 4.11; N, 9.01.

***cis*-1-(3,5-Dinitrobenzoyloxy)-2-ethynylcyclohexane (36).** After the treatment of **23a** (38 mg, 0.10 mmol) according to the above general procedure, the product, dinitrobenzoate, was converted to the corresponding dinitrobenzoate as described above for the synthesis of **12′**. The purification was carried out by column chromatography (SiO_2, 0−8% AcOEt in hexane) to give **36** (12 mg, 36%) as a yellow solid: mp 116−118 °C (yellow crystals from hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24−9.18 (m, 3 H), 5.17 (m, 1 H), 3.11 (m, 1 H), 2.15 (d, 1 H, J = 2.4 Hz), 2.10−1.95 (m, 2 H), 1.86−1.69 (m, 4 H), 1.56−1.43 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.39, 148.27, 133.97, 129.20, 122.02, 82.72, 74.87, 71.23, 32.46, 29.19, 27.77, 22.98, 21.51; LRMS (EI) m/z 318 (M^+). Anal. Calcd for $C_{15}H_{14}N_2O_6$: C, 56.60; H, 4.43; N, 8.80. Found: C, 56.35; H, 4.60; N, 8.89.

***cis*-4-Ethynyl-3-hydroxy-1-tosylpyrrolidine (37).** After the treatment of **25a** (52 mg, 0.10 mmol) or **25b** (45 mg, 0.10 mmol) according to the above general procedure, the resulting residue was purified by column chromatography (SiO_2, 15−35% AcOEt in hexane) to give **37** (21 mg, 80% from **25a**, or 21 mg, 80% from **25b**) as a white solid: mp 120−121 °C (white needles from hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 2 H, J = 8.3 Hz), 7.33 (d, 2 H, J = 8.3 Hz), 4.28 (m, 1 H), 3.71 (dd, 1 H, J = 7.5, 9.8 Hz), 3.55 (ddd, 1 H, J = 1.1, 4.7, 11.5 Hz), 3.31 (dd, 1 H, J = 1.7, 11.5 Hz), 3.22 (dd, 1 H, J = 9.8, 10.0 Hz), 2.89 (m, 1 H), 2.43 (s, 3 H), 2.22 (d, 1 H, J = 2.3 Hz), 2.00 (dd, 1 H, J = 1.1, 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.35, 133.27, 129.40, 127.22, 78.20, 73.97, 71.00, 54.20, 50.03, 36.99, 21.52; LRMS (EI) m/z 265 (M^+). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.77; H, 5.79; N, 5.30.

***cis*-4-Ethynyl-3-hydroxy-1-tosylpiperidine (38).** After the treatment of **27a** (54 mg, 0.10 mmol) or **27b** (46 mg, 0.10 mmol) according to above general procedure, the resulting residue was purified by column chromatography (SiO_2, 15−25% AcOEt in hexane) to give **38** (15 mg, 55% from **27a**, or 19 mg, 68% from **27b**) as a white solid: mp 114−115 °C (white crystals from hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 2 H, J = 8.3 Hz), 7.33 (d, 2 H, J = 8.3 Hz), 3.85 (m, 1 H), 3.32 (dd, 1 H, J = 3.6, 11.7 Hz), 3.18 (m, 1 H), 2.98 (m, 1 H), 2.91 (dd, 1 H, J = 8.3, 11.7 Hz), 2.84 (m, 1 H), 2.44 (s, 3 H), 2.14 (d, 1 H, J = 2.6 Hz), 2.11 (d, 1 H, J = 8.5 Hz), 1.96 (m, 1 H), 1.83 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.36, 133.08, 129.42, 127.25, 81.25, 73.26, 66.27, 48.84, 42.63, 33.13, 27.55, 21.52; LRMS (FAB, positive) m/z 280 (MH^+). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.19; H, 6.19; N, 5.01.

1-*O*-Benzyl-4-pentyn-1,2-diol (39). To a solution of **29a** (44 mg, 0.10 mmol) in toluene (1 mL) was added dropwise Et_3B (1.0 M solution in hexane, 30 μL, 0.030 mmol) under argon atmosphere at room temperature, and the mixture was stirred at room temperature. After 12 h, additional Et_3B (1.0 M solution in hexane, 30 μL, 0.030 mmol), was added, and the mixture was stirred for an additional 60 h. The reaction mixture was treated with TBAF according to the above general procedure. The resulting residue was purified by column chromatography (SiO_2, 15−20% AcOEt in hexane), and then by HPLC (YMC Pack ODS-AM-120-S50, 30 × 300 mm; MeOH, 10 mL/min; room temperature; 254 nm) to give **39** (7 mg, 18%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5 H), 4.58 (s, 2 H), 3.99 (m, 1 H), 3.62 (dd, 1 H, J = 4.1, 9.7 Hz), 3.52 (dd, 1 H, J = 6.8, 9.7 Hz), 2.47−2.45 (m, 3 H), 2.03 (t, 1 H, J = 2.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.38, 128.13, 127.52, 127.41, 79.96, 73.26, 72.55, 70.43, 68.55, 23.41; HRMS (EI) calcd for $C_{12}H_{23}O_2$ 189.0915, found 189.0919 (M^+ − H).

Methyl 2-Deoxy-2-*C*-ethynyl-4,6-*O*-benzylidene-α-D-mannopyranoside (40). After the treatment of **29b** (47 mg, 0.10 mmol) according to the general procedure, the resulting residue was purified by column chromatography (SiO_2, 20% AcOEt in hexane) to give **40** (25 mg, 85%) as a white solid: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.52−7.36 (m, 5 H), 5.61 (s, 1 H), 4.88 (s, 1 H), 4.28 (dd, 1 H, J = 2.6, 8.6 Hz), 4.20 (m, 1 H), 3.97−3.81 (m, 3 H), 3.38 (s, 3 H), 3.31 (m, 1 H), 2.37 (d, 1 H, J = 5.3 Hz), 2.30 (d, 1 H, J = 2.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.80, 128.89, 128.00, 125.90, 101.91, 100.82, 80.11, 79.49, 73.20, 68.60, 66.27, 63.35, 54.97, 40.09; HRMS (EI) calcd for 290.1154, found 290.1160 (M^+).

5-*O*-Acetyl-3-deoxy-3-*C*-ethynyl-1,2-*O*-(1-methylethylidene)-α-D-xylofuranose (41). To a solution of **33a** (38 mg, 0.10 mmol) in toluene (1 mL) was added dropwise Et_3B (1.0 M solution in hexane, 30 μL, 0.030 mmol) under argon atmosphere, and the mixture was stirred at room temperature for 3 h and then at 60 °C for 15 h. After 3 h, the mixture was warmed to 60 °C and stirred for an additional 15 h. The reaction mixture was treated with TBAF according to the above general procedure. The resulting residue was purified by column chromatography (SiO_2, 15−30% AcOEt in hexane) to give a mixture of the desired 3-*C*-ethynylated product and **32** (27 mg, the ratio was 2:1) as a white solid. A solution of the obtained mixture of the ethynylated product and **32** (27 mg), Ac_2O (28 μL, 0.3 mmol), Et_3N (42 μL, 0.3 mmol), and DMAP (5 mg, 0.04 mmol) in MeCN (2 mL) was stirred at room temperature for 3 h. The solvent was evaporated, and the residue was purified by column chromatography (SiO_2, 15% AcOEt in hexane) to give **41** (8 mg, 31%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (d, 1 H, J = 3.6 Hz), 4.75 (d, 1 H, J = 3.6 Hz), 4.43−4.30 (m, 3 H), 3.13 (dd, 1 H, J = 2.6, 4.1 Hz), 2.22 (d, 1 H, J = 2.6 Hz), 2.10 (s, 3 H), 1.52 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.27, 111.82, 105.01, 84.71, 77.50, 75.94, 73.96, 63.88, 39.72, 26.53, 26.16, 20.81; LRMS (EI) m/z 241 (MH^+). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.22; H, 6.91.

1-[5-*O*-(4-Methoxytrityl)-2-deoxy-2-iodo-3-*O*-(trimethylsilyl)ethynyldimethylsilyl-β-D-*ribo*-pentofuranosyl]uracil (43). Compound **37** (285 mg, 78%) was obtained as a pale yellow foam from **42** (251 mg, 0.40 mmol) as described above for the synthesis of **10a**, after purification by column chromatography (SiO_2, 25−50% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1 H), 7.83 (d, 1 H, J = 7.9 Hz), 7.39−6.85 (m, 14 H), 6.39 (d, 1 H, J = 5.9 Hz), 5.31 (d, 1 H, J = 7.9 Hz), 4.50 (m, 1 H), 4.26 (m, 1 H), 4.10 (m, 1 H), 3.81 (s, 3 H), 3.55 (dd, 1 H, J = 2.6, 11.2 Hz), 3.48 (dd, 1 H, J = 2.0, 11.2 Hz), 0.36 (s, 3 H), 0.23 (s, 3 H), 0.09 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.56, 158.76, 149.96, 143.55, 143.26, 139.33, 134.28, 130.39, 128.30, 128.05, 127.36, 127.34, 116.39, 113.32, 109.63, 102.52, 90.96, 87.63, 84.38, 71.89, 61.99, 55.28, 31.79, 0.59, 0.46, −0.32; LRMS (FAB, positive) m/z 781 (MH^+). Anal. Calcd for $C_{36}H_{41}IN_2O_6Si_2$: C, 55.38; H, 5.29; N, 3.59. Found: C, 55.37; H, 5.32; N, 3.44.

1-(3,5-*O*-Diacetyl-2-deoxy-2-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)uracil (44). To a solution of **43** (78 mg, 0.10 mmol) in toluene (1.0 mL) was added dropwise Et_3B (1.0 M solution in hexane, 30 μL, 0.03 mmol) under argon atmosphere, and the mixture was stirred at room temperature for 5 h. After addition of TBAF (1.0 M solution in THF, 300 μL, 0.30 mmol), the resulting mixture was stirred for an additional 2 h, and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, 5−10% MeOH in $CHCl_3$) to give crude **4** including some impurities. A mixture of the solid and Ac_2O (84 μL, 0.90 mmol) in pyridine (1 mL) was stirred at room temperature for 24 h, and then evaporated. The residue was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), evaporated. The residue was purified by column chromatography (SiO_2, 0−4%

MeOH in $CHCl_3$) to give **44** (23 mg, 67%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (br s, 1 H), 7.37 (d, 1 H, J = 8.2 Hz), 6.26 (d, 1 H, J = 8.2 Hz), 5.83 (dd, 1 H, J = 2.1, 8.2 Hz), 5.33 (dd, 1 H, J = 2.3, 6.2 Hz), 4.38−4.28 (m, 3 H), 3.32 (m, 1 H), 2.29 (d, 1 H, J = 2.3 Hz), 2.19 (s, 3 H), 2.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.65, 169.48, 162.17, 149.78, 138.37, 103.40, 87.65, 80.91, 75.11, 74.19, 72.87, 63.30, 39.91, 20.79, 20.72; HRMS (FAB, positive) calcd for $C_{15}H_{17}N_2O_7$ 337.1036, found 337.1035 (MH^+).

1-(2-Deoxy-2-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)uracil (6). A mixture of **44** (50 mg, 0.15 mmol) and K_2CO_3 (4 mg, 0.03 mmol) in MeOH (1.5 mL) was stirred at room temperature for 15 h, and then evaporated. The residue was purified by column chromatography (SiO_2, 2−10% MeOH in $CHCl_3$) to give **6** (37 mg, 98%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.26 (br s, 1 H), 7.81 (d, 1 H, J = 8.1 Hz), 6.09 (d, 1 H, J = 8.8 Hz), 5.71 (d, 1 H, J = 5.7 Hz), 5.70 (d, 1 H, J = 8.1 Hz), 5.10 (t, 1 H, J = 5.1 Hz), 4.18 (m, 1 H), 3.86 (m, 1 H), 3.53 (m, 2 H), 3.22 (m, 1 H), 3.08 (d, 1 H, J = 2.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.78, 150.56, 140.09, 102.51, 86.97, 86.19, 78.15, 76.10, 72.04, 61.38, 41.01; HRMS (EI) calcd for $C_{11}H_{12}N_2O_5$ 252.0746, found 252.0766 (M^+).

1-(2-Deoxy-2-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)cytosine (7). A mixture of **44** (111 mg, 0.33 mmol), TPSCl (200 mg, 0.66 mmol), DMAP (81 mg, 0.66 mmol), and Et_3N (92 μL, 0.66 mmol) in MeCN (3.3 mL) was stirred at room temperature for 15 h. After addition of queous NH_4OH (25%, 3.3 mL), the resulting mixture was stirred at the room temperature for 10 h, and then evaporated. The residue was purified by silica gel column chromatography (0−4% MeOH in $CHCl_3$) then by C18 reversed phase column chromatography (1.5 × 10 cm, 50% MeOH in H_2O) to give **7** (73 mg, 88%) as a white solid: mp 230 °C (decomposed, colorless crystals from MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, 1 H, J = 7.5 Hz), 7.25 (br s, 1 H), 7.22 (br s, 1 H), 6.13 (d, 1 H, J = 8.5 Hz), 5.73 (d, 1 H, J = 5.3 Hz), 5.61 (d, 1 H, J = 7.5 Hz), 5.04 (t, 1 H, J = 5.3 Hz), 4.15 (m, 1 H), 3.82 (m, 1 H), 3.51 (m, 2 H), 3.14 (m, 1 H), 3.01 (d, 1 H, J = 2.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.31, 155.13, 141.04, 94.72, 87.10, 86.43, 78.79, 75.71, 71.92, 61.46, 41.20; LRMS (FAB, positive) m/z 252 (MH^+). Anal. Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.40; H, 5.18; N, 16.66.

Acknowledgment. This investigation was supported by a Grant-in-Aid for Creative Scientific Research (13NP0401) and a Grant-in-Aid for Scientific Research (S.S.) from the Japan Society for Promotion of Science. We are also grateful to Ms. H. Matsumoto, A. Maeda, and S. Oka (Center for Instrumental Analysis, Hokkaido University) for technical assistance with NMR, MS, and elemental analyses.

Supporting Information Available: Experimentally details for the synthesis of TEDMS−NMe_2, EDMS−Cl, **18**, **24**, **26**, **28**, **30**, and **32**, and ^{1}H NMR charts of **6**, **18**, **30**, **33a**, **39**, **40**, **44**, and **S12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0206667