Experimental Section

1a: $[Pd(dba)_2]$ (288 mg, 0.50 mmol) and P(1-Ad)P*t*Bu_2[22] (560 mg, 2.00 mmol) were stirred in toluene (15 mL) in a vial for 3 h. After this time, $[PdBr_2(cod)]$[23] (378 mg, 1.01 mmol) was added, and the mixture was stirred for an additional 4 h. The reaction volume was concentrated by half, and the contents were filtered through a glass-fritted funnel. The dark-green solid was washed three times with acetone (10 mL) and dried under vacuum. Yield: 498 mg (0.533 mmol, 53.4 %); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 1.39$ (t, 36 H, 6 Hz, *t*Bu), 1.47–1.61 (br m, 12 H, CH_2), 1.77 (br s, 6 H, CH), 2.32 ppm (br s, 12 H, CH_2); ^{13}C NMR (100 MHz, C_6D_6, 40 °C): $\delta = 29.4$ (t, 4.0 Hz, CH_2), 33.0 (br s, CH_2), 36.8 (t, 1.8 Hz, C Ad), 36.9 (s, CH_3), 41.7 (br s, CH), 42.0 ppm (br s, *C*Me_3); ^{31}P NMR (202 MHz, C_6D_6): $\delta = 88.0$ ppm (s); Anal. calcd. for $C_{36}H_{66}Br_2P_2Pd_2$: C 46.32, H 7.13, Br 17.12; found: C 45.94, H 7.03, Br 17.02.

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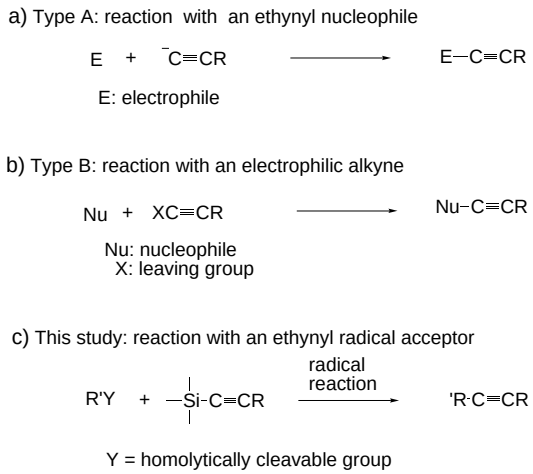
A New Entry to the Stereoselective Introduction of an Ethynyl Group by a Radical Reaction: Synthesis of the Potential Antimetabolite 2′-Deoxy-2′-*C*-ethynyluridine**

Makoto Sukeda, Satoshi Ichikawa, Akira Matsuda, and Satoshi Shuto*

Ethynyl groups are present in many biologically active compounds, including clinically useful drugs,[1] and are also valuable in organic synthesis because the triple bond can be converted into a variety of functional groups.[2] Accordingly, much effort has been expended to develop methods for introducing ethynyl and/or substituted ethynyl groups into compounds to produce alkynes by C–C bond formation.[2] These methods can be generally classified as Type A, reactions of ethynyl nucleophiles such as acetylides or their congeners (Scheme 1 a), and Type B, reactions of electrophilic alkynes bearing a leaving group (Scheme 1 b). Type A includes reactions of alkynyl metals with carbon electrophiles[3] and transition metal catalyzed cross-coupling reactions with alkyne derivatives.[4] Type B is typified by reactions between an alkynyl halide and a carbon nucleophile, which appear to proceed by an addition–elimination mechanism.[5] Although these are very effective, regio- and stereoselective introduction of an ethynyl group at aliphatic carbon centers is sometimes troublesome.



Scheme 1. Methods for introducing ethynyl and substituted ethynyl groups.

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[**] Nucleosides and Nucleotides, Part 216. This work 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. For Part 215, see: N. Minakawa, D. Kaga, Y. Kato, K. Endo, M. Tanaka, T. Sasaki, A. Matsuda, *J. Chem. Soc. Perkin Trans. 1*, 2002, 2182–2189.

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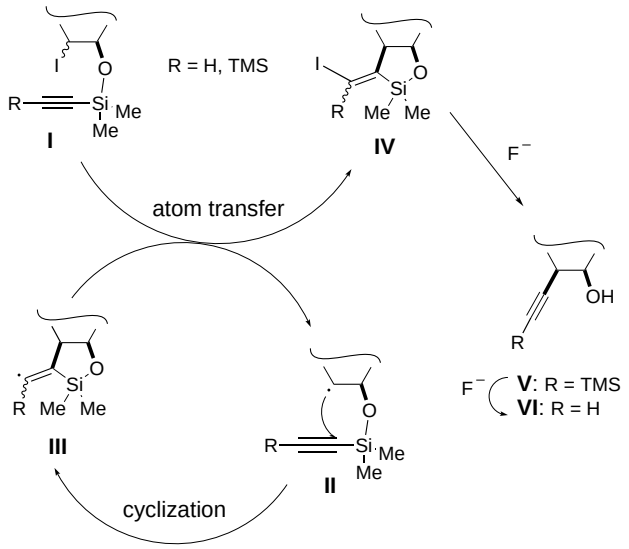
In the course of our synthetic study on antitumor branched-sugar nucleosides,[6] a new method for the stereoselective introduction of an ethynyl group was needed. Here we describe a new method for introducing ethynyl groups by adaption of an atom-transfer radical cyclization reaction[7] with an ethynylsilyl group (Scheme 1c), which was devised on the basis of our recent studies on radical reactions with a silicon tether,[8,9] and is clearly different from the previous ionic reaction method.

Our strategy that uses ethynyldimethylsilyl (EDMS) or [2-(trimethylsilyl)ethynyl]dimethylsilyl (TEDMS)[10] ethers of iodohydrins **I** as reaction substrates is shown in Scheme 2. The



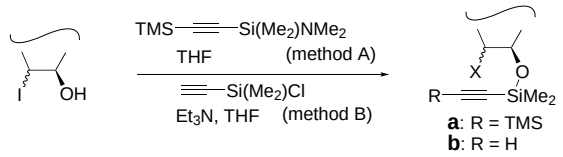
Scheme 2. Ethynyl group introduction by atom-transfer radical cyclization and subsequent elimination. TMS = trimethylsilyl.

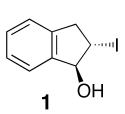
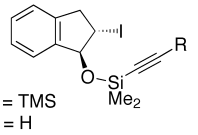
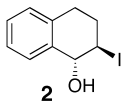
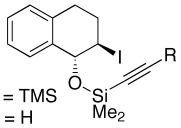
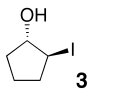
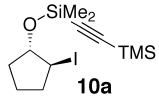
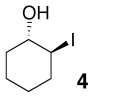
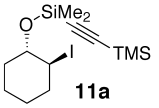
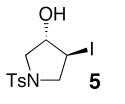
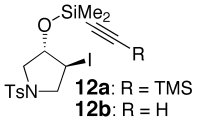
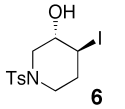
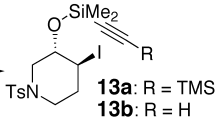
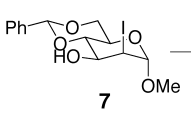
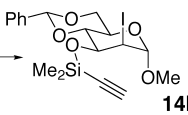
radical **II** generated from **I** preferentially undergoes 5-*exo* cyclization to produce the radical **III**. In the absence of a hydrogen source, **III** would abstract the iodine atom of another substrate **I** to regenerate the radical **II** along with the atom-transfer radical cyclization product **IV**.[11] Turnover of this scheme would accumulate the desired product **IV**, subsequent treatment of which with fluoride ion would promote elimination[12] to give the desired ethynyl product **V** or **VI**.

The reaction was carried out with EDMS and TEDMS ethers of a variety of iodohydrins as substrates, which were prepared with EDMS-Cl[13] or TEDMS-NMe_2[14] (Table 1). We first examined the radical atom-transfer reaction with the TEDMS and EDMS ethers of 2-iodoindanol (**8a** and **8b**) under various conditions, and found that when the substrate was treated with Et_3B (0.3 equiv) at room temperature in toluene under argon, the expected atom-transfer cyclization proceeded effectively, and immediate treatment of the product, without purification, with tetrabutylammonium fluoride (TBAF) gave the desired ethynyl product **15**[15] in high yield (Table 2, entries 1 and 2).

By using the same procedure, the reactions with various TEDMS and EDMS ethers were examined, and the results are summarized in Table 2. The reactions with the EDMS and

Table 1. Preparation of the ethynylsilyl ethers.



Iodohydrin	Method	Ethynylsilyl ether	Yield [%]
	A or B	 **8a**: R = TMS **8b**: R = H	83
	A or B	 **9a**: R = TMS **9b**: R = H	71 67
	A	 **10a**	70 78
	A	 **11a**	90
	A or B	 **12a**: R = TMS **12b**: R = H	63 quant.
	A or B	 **13a**: R = TMS **13b**: R = H	77 quant.
	B	 **14b**	90

TEDMS ethers of *trans*-2-iodotetrahydronaphthol (**9a** and **9b**) as well as pyrrolidine and piperidine derivatives (**12a**, **12b**, **13a**, and **13b**) effectively produced the products of atom-transfer cyclization and subsequent elimination **16**, **19**, and **20**, respectively, in good yields (entries 3, 4, and 7–10). On the other hand, the reactions with TEDMS ethers of 2-iodocyclopentanol (**10a**) and 2-iodocyclohexanol (**11a**) gave the corresponding 2-ethynyl products **17** and **18** in only moderate yields (entries 5 and 6). In these reactions, the comparatively low yields of isolated products might be explained by their volatility, since TLC analysis suggested that both of the reactions seemed to proceed effectively. The reaction was used to synthesize a branched sugar; treatment of the EDMS ether of the 2-deoxy-2-iodo-D-mannoside **14b** by the above procedure furnished the expected 2-ethynyl product **21** in 85% yield. Thus, it appears that the atom-transfer radical cyclization and subsequent elimination effectively occurs in iodohydrin substrates with five- or six-membered rings.

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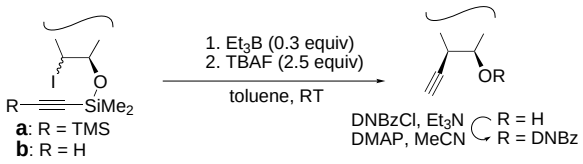
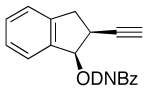
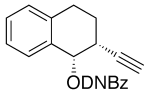
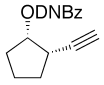
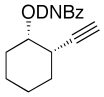
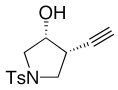
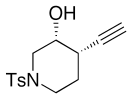
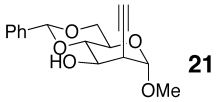
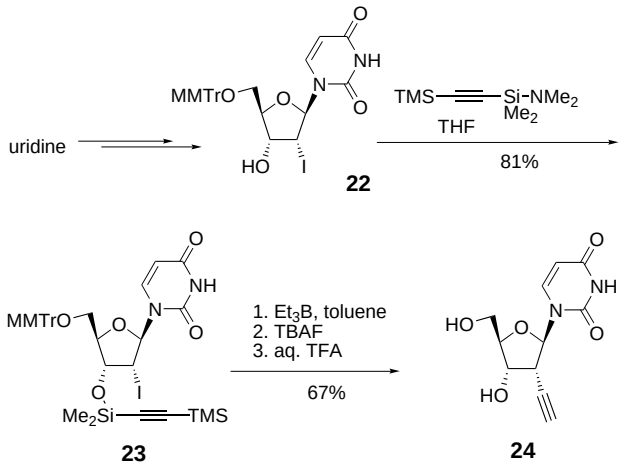
Table 2. Atom-transfer radical cyclization and subsequent elimination reaction of the ethynylsilyl ethers.[a]



Entry	Substrate	Product[b]	Yield [%]
1	**8a**	 **15**	87
2	**8b**		88
3	**9a**	 **16**	83
4	**9b**		86
5	**10a**	 **17**	33
6	**11a**	 **18**	36
7	**12a**	 **19**	80
8	**12b**		80
9	**13a**	 **20**	55
10	**13b**		68
11	**14b**	 **21**	85

[a] DMAP = 4-dimethylaminopyridine, DNBz = 3,5-dinitrobenzoyl. [b] In entries 1–4, the atom-transfer radical cyclization product was isolated after conversion to the corresponding 3,5-dinitrobenzoate (R = DNBz).

Finally, we applied the reaction to the synthesis of 2′-deoxy-2′-*C*-ethynyluridine (**24**), designed as a potential antimetabolite (Scheme 3). When the 2′-deoxy-2′-iodo-3′-*O*-TEDMS-uridine derivative **23**, prepared from known **22**,[6] was subjected to the above procedure, the desired **24** was obtained in 67% yield.



Scheme 3. Synthesis of 2′-deoxy-2′-*C*-ethynyluridine (**24**). TFA = trifluoroacetic acid, MMTr = monomethoxytrityl.

In summary, we have developed an efficient method for introducing an ethynyl group by means of an atom-transfer radical cyclization reaction. This is the first example in which a radical reaction was used for introducing an ethynyl group.

Experimental Section

General procedure for the atom-transfer radical cyclization and subsequent elimination reaction with Et_3B: Et_3B (1.0 M in hexane, 30 μL, 0.030 mmol) was added dropwise to a solution of a substrate (0.10 mmol) in toluene (1 mL) under argon, and the mixture was stirred at room temperature for 2 h. After addition of TBAF (1.0 M in THF, 250 μL, 0.25 mmol), the mixture was stirred at room temperature for 2 h, evaporated, and purified by column chromatography on silica gel.

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